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Antigen Specific and Cross-Reactive T Cells in Protection and Disease

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Summary

Human T cells have a diverse T cell receptor (TCR) repertoire that endows them with the ability to identify and defend against a broad spectrum of antigens. The universe of possible antigens that T cells may encounter, however, is even larger. To effectively surveil such a vast universe, the T cell repertoire must adopt a high degree of cross-reactivity. Likewise, antigen-specific and cross-reactive T cell responses play pivotal roles in both protective and pathological immune responses in numerous diseases. In this review, we explore the implications of these antigen-driven T cell responses, with a particular focus on CD8+ T cells, using infection, neurodegeneration, and cancer as examples. We also summarize recent technological advances that facilitate high-throughput profiling of antigen-specific and cross-reactive T cell responses experimentally, as well as computational biology approaches that predict these interactions.

Keywords

Antigen-specific T cells; T cell cross-reactivity; Cancer; Infection; Vaccination; Neurodegenerative diseases

TCR repertoire size, T cell number, and antigen space

The discovery of TCR genes almost 40 years ago marks the beginning of an exciting era in immunology[1,2]. Using V(D)J recombination, human T cells generate an enormously large repertoire of T cell antigen receptors (TCR). The estimated potential diversity could be in the range of 2×10^{19} unique receptors,[3,4] orders of magnitude larger than the TCR repertoire of any individual. Jenkin et al[5], did an exhaustive count of naïve T cells in mice, estimating that an adult mouse has about 8×10^{7} α/β TCR+ T cells in the secondary lymphoid organs and another 5×10^{6} in the blood. Of these, about 70% of the cells are of a naïve

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phenotype [5]. Thus, about 2.6×10^7 non-naïve T cells exist in secondary lymphoid organs and blood of healthy mice under specific pathogen-free conditions. Tissue resident memory T cells constitute a major population in both mice and humans[6,7]. Using a quantitative immunofluorescence microscopy[8] strategy to analyze the distribution of CD8 T cells in a TCR (P14) transgenic mouse 120–150 days after LCMV infection, it was estimated that about 43% of the memory P14 pool was localized in secondary lymphoid organs, 29% in circulating blood and marginated pool (including i.v. Ab^+ cells from all tissues examined), and 28% in nonlymphoid tissues (including i.v. Ab^- cells within liver, lung, kidney, pancreas, salivary gland, uterus, vagina and cervix, small intestine, large intestine, stomach, and thymus). Combining these two pieces of information and taking 2:1 for CD4 to CD8 T cell ratio, there are about 0.9×10^7 T cells in nonlymphoid tissues. This puts the total number of T cells in a mouse to be around 9.4×10^7. By extrapolation based on body weight, an adult human has about 4.7×10^{11} T cells, which is in the same order of magnitude estimated by human T cell weight[9,10].

Don Mason showed an elegant derivation of the size of potential antigen space by considering the fraction of possible peptide binding to MHC[11]. But even a conservative estimate of 12 amino acids in peptide length and 20 possible amino acids in each position puts a rough estimate of the potential antigen space to 4.1×10^{15}. This is about four orders of magnitude larger than the total number of T cells in a human. Thus, in order to avoid holes in TCR coverage, an individual T cell must recognize at least 10,000 antigens. The degree of cross-reactivity is likely to increase as the T cell clonal expansion significantly reduces the number of TCR diversity in the total number of T cells each individual harbors[12–18]. Another complexity is that single antigens are recognized by polyclonal T cells. It is extremely inefficient for each antigen to be recognized by only one cell as studies in mice and humans in both CD4 and CD8 T cell compartments[12–18] have shown that precursor T cell frequency is about 1 in 10^5 to 1 in 10^6.

As a result, the interactions between a TCR repertoire and the antigen space can be described as a complex and dynamic mesh network, where multiple TCRs can recognize a single antigen and multiple antigens can be recognized by a single TCR. The interactions between TCRs and antigens in a given context greatly impact how T cells surveil, contribute to disease protection, or become dysregulated in disease. Exploring examples from TCR-antigen interaction across infection, neurodegeneration, and cancer highlights the complexity and importance of understanding the context-dependent antigen specific and cross-reactive T cell response. Therefore, this review will cover data published across these fields to explore: (1) Methodologies to identify antigen-specific T cells and their fundamental properties such as TCR affinity and functionality; (2) Examples of variable antigen-specific and cross-reactive T cell responses in infection, neurodegeneration, and cancer; (3) Computational approaches in TCR-antigen binding prediction; (4) An outlook of experimental and computational needs to facilitate TCR-antigen discovery.

Technologies in peptide antigen and antigen-specific TCR discovery

Since the paradigm-shifting finding that TCR recognizes peptides presented by MHCs[19–26], there has been a widespread interest to identify peptide antigens and their cognate T

cells. This effort has been facilitated by the development of mass spectrometry[27]. Mass-spectrometry-based immunopeptidomics has also enabled the discovery of noncanonical antigens[28]—antigens derived from sequences outside protein-coding regions, such as cryptic peptide discovered in neurodegenerative diseases and cancer (see below), or generated by noncanonical antigen-processing mechanisms, such as some of the cancer antigens (see below) or fusion peptides, such as those discovered in type 1 diabetes[29]. Recently, tremendous advances have been made in resolving proteins in a small number of cells. Multiple improvements have been made to increase the sensitivity and throughput of single cell proteome measurement[30]. At the same time, various technologies have been developed for single-molecule protein sequencing[31]. These technological advancements will undoubtedly change the landscape of antigen discovery. On the other side, many approaches to exchange peptides bound to MHC molecules have been developed[32–36] as well as higher valency of peptide-MHC (pMHC) multimers[37,38] and affinity matured MHC-II molecules[39,40] to enhance the binding to lower affinity TCRs, especially on $CD4^+$ T cells. Combining technologies from these areas will open many possibilities of high-throughput antigen-specific and cross-reactive TCR discovery in future studies.

There are two main categories of methods for antigen-specific TCR discoveries: pMHC multimer binding based and functional test based. In the last decade, significant progress was made in both categories and was comprehensively summarized in a recent review by Joglekar et al[41]. The application of some of these methods is discussed throughout the current review. Recently, there are additional technologies developed in pairing TCR with antigens. Dahotre et al[42] developed a droplet digital PCR based method to count DNA barcoded pMHC bound on T cells, which could be more accurate in numerating antigen specific T cells than sequencing-based methods. Ma et al[43] combined DNA-barcoded pMHC tetramer linked TCR sequencing with single cell gene expression and DNA-barcoded phenotyping antibodies to develop a multi-dimensional integrated profiling of antigen-specific T cells, named TetTCR-SeqHD. TetTCR-SeqHD enables the direct profiling of phenotypes and functional states of antigen specific T cells without any stimulation, which is critical in studying the roles of antigen specific T cells to disease initiation and pathogenesis. Liu et al[44] developed a FucoID method that uses glycosyltransferase-mediated tagging to label and capture antigen-specific T cells in a cell interaction-dependent manner. Using an updated *in vitro* T cell expansion method, Arnaud et al[45] developed NeoScreen to increase the efficiency of *in vitro* expansion of cancer antigen specific T cells infiltrated to tumor. This, in combination with the above technologies mentioned, could significantly increase cancer antigen specific TCR discovery. V-CARMA[46] and ENTER[47] represent another group of methods recently developed that take advantage of lentiviral-based display and delivery platform to identify and isolate antigen-specific T cells, and deliver cell-specific genetic cargo at the same time. Although the throughput of generating pMHC expressing viral particles is still limited, V-CARMA and ENTER are great methods to deliver cargo to T cells in an antigen-specific manner.

In addition to chemical interactions, mechanical interactions among macromolecules have emerged as another modality that impacts receptor-ligand interactions. A classic example can be found within adhesion molecules, such as selectins and integrins, that need to overcome sheer stress when helping leukocytes exit blood vessels. Initial increase of force

results in an increase of bond lifetime between adhesion molecules and their ligands (catch phase). However, further increase of force results in a decrease of bond lifetime between adhesion molecules and their ligand (slip phase). Thus, the molecular interactions that contain both catch phase and slip phase are known as “catch bonds”, while the molecular interactions that contain only the slip phase are known as “slip bonds”. Slip bonds[48] and catch bonds[49] were predicted theoretically in 1978 and 1988, respectively. Although slip bonds were detected in many molecules, the catch bond was only first detected by Cheng Zhu’s lab in 2003 in selectins[50] then again in integrins[51] when bond lifetime measurements were developed and implemented. Later, it was demonstrated that TCRs also exhibit a catch-bond property when interacting with agonist and partial agonist ligands, but exhibit slip bonds when interacting with antagonist and weak agonist ligands[52]. Recently, it was shown that catch bonds could be used to distinguish specific antigens from cross-reactive antigens[53] (see below). Thus, catch bond analysis could be integrated into TCR based therapeutic development.

Large scale of epitope screens on pathogens

Understanding the epitopes that T cells target during infection and vaccination is of great value to understanding the T cell responses and designing better vaccines. Using a variety of approaches, including multiplexing pMHC multimers with flow cytometry[54], mass cytometry[55–57] or NGS[58] as readouts, immunopeptidomics[59], activation-induction[60–63], antigen presentation array-based[64] assays, and others reviewed recently[41], a litany of T cell targets to a variety of pathogens have been unveiled. These types of screens have laid the groundwork to deepen our understanding of the principles that govern TCR:pMHC interactions, the phenotypes that ensue, and how to intervene in order to induce more favorable outcomes.

SARS-2 and hCOVs/pre-existing immunity

One perplexing aspect of COVID-19 is the wide variability in disease severity. An early hypothesis was that memory specific to other coronaviruses that cause the common cold (hCOVs) could cross-react to SARS-CoV-2 and provide some protection. Early investigation of infections in healthcare workers revealed that individuals with abortive seronegative SARS-CoV-2 titers exhibited an expansion of pre-existing SARS-CoV-2 specific T cells in the blood[65]. A later study built on this rationale, finding T cells specific to the same antigens in the airways of pre-pandemic samples that correlated to the response to corresponding hCOV antigens[66].

Several other studies have also corroborated the existence of pre-existing T cell immunity in the blood. Using both pMHC tetramer and stimulation-based assays, several groups have observed non-naïve, spike and non-spike specific T cells in the blood of pre-pandemic individuals over several HLA backgrounds[67–69]. These SARS-CoV-2 specific cells were often of an effector memory phenotype and could exhibit T cell effector functions, suggesting a potential capacity to play a role during infection. In one of these studies, Schulian, et al also showed that these cross-reactive TCRs were of comparable affinity to SARS-CoV-2 and hCOV specific TCRs. Using flow cytometry[70] and single cell sequencing-

based tetramer approaches[58], two independent studies revealed that the degree of pre-existing cross-reactivity was dependent on the HLA background. Both studies implicate a nucleocapsid protein-derived, HLA-B*07:02-restricted (B7/NP_{105}) epitope as highly dominant, eliciting expanded T cells in both pre-existing and post-infection repertoires (Table 1). Interestingly, both studies report a limited number of shared TCR features across donors compared to other SARS-CoV-2 epitopes, underpinned by distinct V/J gene usage and promiscuous α/β chain pairing. Nguyen et al[70] also observed differences in the number of N-insertions in the CDR3s of pre-pandemic versus post-infection TCRs specific to B7/NP_{105}, suggesting differential pressures on the repertoires before and after COVID-19.

Given that B7/NP_{105} is only a single amino acid point mutation from other beta coronaviruses, it is possible that differences in the antigen presentation capacity of different HLA backgrounds may dictate the degree of pre-existing immunity, thereby impacting disease severity. In fact, another large study found an association between mild disease and a B7/NP_{105} response[71]. In addition to observing usage of pre-existing immunity, high functional avidity, and effector functions, the authors also reported stronger maintenance of memory in convalescence compared to other epitopes. Possibly related to the abortive seronegative healthcare workers described early in the pandemic[65], Kendu et al reported a larger number of IL2-secreting nucleocapsid specific T cells in individuals before and after close contact COVID-19 exposures who remained PCR-negative versus those who tested positive[72]. Although the authors did not test a direct relationship with HLA background, it is possible that some of the protection provided in their study was due to a strong response by pre-existing B7/NP_{105} specific T cells. It is thus possible that prior stimulation through prior encounters with hCOVs causes B7/NP_{105} specific cells to engage in a more robust secondary immune response and long-lived phenotypic state. Furthermore, Nguyen et al also showed that B7/NP_{105} specific T cells can respond to the variants of concern (VOCs) at the time (Alpha, Beta, Gamma, Delta), suggesting a capacity to continue providing protection under the selective pressure of a mutating virus[70].

Cross-reactivity between SARS-CoV-2 and persistent viruses

Several risk factors have emerged as predictors of developing severe COVID-19. HIV infection[73], cancer[74], Type 1 and 2 Diabetes[75], age[76], and obesity[77] are some of many pre-dispositions associated with cases of severe COVID-19. One less clear, yet interesting, example of COVID-19 comorbidity is infection with persistent viruses. Persistent viral infections, such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV), are common in the population. In health they generally pose no threat, but in the immunocompromised and in infants they can present serious problems[78,79]. Infection with persistent viruses have also been linked to autoimmune diseases, such as multiple sclerosis[80,81], revealing their capacity to elicit aberrant immune programs. The specific mechanisms of the observed immune aberrancy, however, remains unclear.

Infection with persistent viruses has also been linked to broad phenotypic changes in T cells[82,83]. It is well established that CMV infection decreases the naïve T cell repertoire, as well as increases senescent memory cells, which has been reviewed extensively[84]. These senescent memory cells often have an impaired ability to divide upon stimulation.

Interestingly, these broad phenotype changes have often been paralleled to changes that accumulate with age. In COVID-19, CMV infection has been highlighted as a potential risk factor for developing severe disease, specifically in non-geriatric patients (< 60 years)[85]. Such a phenomenon may be a consequence of CMV's imprinting of an aged-like repertoire on younger immune systems. Interestingly, an independent study observed $CD4^+$ and $CD8^+$ T cells that could cross-react with both CMV and SARS-CoV-2 epitopes in SARS-CoV-2 unexposed individuals[86]. The authors also specifically delineated HLA-B*35:01-restricted $CD8^+$ T cells binding to CMV pp65 and SARS-CoV-2 Spike epitopes in multiple individuals, rooted in a public TCR. Although the peptides share little homogeny (22%, Table 1), *in silico* structure analysis revealed a similar backbone conformation may be adopted in both pMHC structures. These cross-reactive T cells generally took either effector memory (EM) or effector memory RA (EMRA) phenotypes but did not activate during acute COVID-19. It is possible that these cross-reactive T cells bear a degree of immune senescence imparted by CMV infection that prevents them from participating in clearance of SARS-CoV-2. In support of this paradigm, another study observed a higher number of $CD57^+$ (a marker indicative of cellular senescence in $CD8^+$ T cells[87]) precursor SARS-CoV-2 specific $CD8^+$ T cells in unexposed CMV seropositive versus seronegative individuals, mirroring that of the aged immune system[88]. A deeper understanding of how persistent viruses affect independent immune responses mechanistically could lead to better therapeutic interventions in cases of comorbidities.

T cell immunity to viral mutagenesis

Preservation of immunity to mutating viral strains is of great concern in vaccinology. Accumulation of mutations that abrogate binding of the repertoire can significantly cripple a vaccine's effectiveness. A recent update in COVD-19 mRNA vaccines toward a bivalent formulation, containing both ancestral and omicron strains, is one such example that has been used in attempts to combat a drifting virus. Another prominent example is that of influenza vaccination, which requires annual updates to keep pace with a rapidly mutating virus. Due to the extensive length of production time in manufacturing seasonal influenza vaccines, variability in mutation predictions can lead to a wide range in efficacy. These inconsistencies highlight a critical need to deepen our knowledge of the immune response to mutagenesis. On the other end of the spectrum, HIV mutates at such a rapid rate that even seasonal vaccine updates would not be feasible. Such a phenomenon is one of the reasons that has made design of effective HIV vaccines an immense challenge. The following section will discuss mutation rates in SARS-CoV-2, influenza, and HIV and some of their immunological consequences.

Tracking propagation of mutations within the SARS-CoV-2 genome has thus been of great concern since its emergence in 2019. Due to proofreading machinery, SARS-CoV-2 accumulates mutations at a modest rate relative to other viruses – roughly 10^{-5} to 10^{-3} substitutions per base per infection cycle[92]. The sheer number of infections in the population (>760 million confirmed cases globally as of March 2023 according to the WHO health Emergency Dashboard); however, has led to many opportunities for the virus to mutate. As such, several variants of concern (VOCs) have emerged, often followed by cycles of increased infection rates. Several studies characterizing vaccine-induced antibody responses

and therapeutic monoclonal antibodies have revealed a significant reduction in neutralization toward most VOCs, particularly toward the more recent Omicron lineages[93,94]. Newer bivalent formulations of the vaccine, which include Omicron spike glycoprotein-encoding mRNA, also do not appear to improve antibody neutralization compared to the old formulation[95,96]. In contrast, T cell immunity has been revealed to remain durable against Omicron lineages[97–99], even contributing to preventing infection in some cases[100].

A lack of mutations on immundominant epitopes may be a substantial reason that the T cell response to SARS-CoV-2 remains durable. To date, only five of the top twenty most cited immune epitope database (IEDB)[101] SARS-CoV-2 spike-derived epitopes have been mutated in any dominant lineage – most of which are single amino acid point mutations. Building on this paradigm, a recent study revealed that a strong T cell response to these unmutated, immunodominant epitopes was associated with milder COVID-19[38]. One specific example of a mutated SARS-CoV-2 immunodominant epitope, however, is an HLA-A*24:02-restricted ($A24/S_{448}$) epitope. In Delta and BA.4/5 lineages, an L452R substitution has been shown to increase infectivity[89] (Table 1). Furthermore, CD8+ T cells from vaccinated donors respond poorly to the mutated epitope, suggesting lack of consistent cross-reactivity in the vaccine-induced repertoire[102]. It is thus possible that if SARS-CoV-2 continues to accumulate mutations, new variants will emerge that will not be durably cross-protected by previous T cell immunity.

Mutations in influenza A virus (IAV) are also a major concern. Although a $CD8^+$ T cell response is not generally elicited by seasonal influenza vaccination, universal T cell epitopes have been characterized through immunopeptidomics[59]. Furthermore, as with SARS-CoV-2, T cell contribution during IAV infection is an important aspect of viral clearance[103]. T cells cross-reactive to several IAV strains have also been characterized structurally and via flow cytometry[90] (Table 1), revealing a structural conservation of pMHC amongst the variants that likely underpins the high degree of observed cross-reactivity in the repertoire. Such a finding supports the argument for T cell consideration in seasonal influenza vaccination. In fact, significant effort has been directed toward the development of universal flu vaccines that could provide an immunological safeguard in the event of vaccine mismatches. Several clinical and pre-clinical studies involving T cell-based influenza vaccines have been reviewed recently[104]. Wide-spread implementation of safe and effective versions of these vaccines could lead to dramatic changes in the way we develop and think about vaccinology in general.

Even more so than SARS-CoV-2 and influenza, HIV provides an example that has been immensely challenging to design effective vaccines against. The high degree replicative errors within in the HIV genome makes it a particularly problematic example of mutation-based immune evasion. Unlike SARS-CoV-2, HIV contains quite promiscuous replication machinery. Being so, HIV-1 has been shown to accumulate on the order of 0.1 to 1 mutations per genome replication[105–108]. Such a high mutation burden is one of the major contributing factor of CD8+ T cell-mediated immune escape during chronic HIV infection[109].

Although rare, there have been many cases of HIV-infected individuals, categorized as elite controllers and long-term non-progressors, that are capable of controlling virus below detection without therapeutic intervention for 10+ years[110]. An early connection between viral control and $CD8^+$ T cells came from a study that linked long-term non-progressors to HLA-B*57:01[111]. The functional properties of $CD8^+$ T cells have also been associated with viral control. Specifically, the ability to proliferate[112] and kill[113] upon stimulation with HIV antigens was consistently greater in controllers versus progressors. In contrast, cellular activation alone was not indicative of control as activated cells from progressors often exhibited exhausted phenotypes. Furthermore, HIV-specific $CD8^+$ T cells remained exhausted after prolonged anti-retroviral treatment (ART)[114]. Although the imprinting of a defective $CD8^+$ T cell phenotype is apparent, the mechanism of this imprinting remains unclear. Do these dysfunctional phenotypes in HIV mirror those observed in persistent viruses, other chronic infections, or uncontrolled cancer? Teasing apart the presence or lack of these inter-disease relationships could prove incredibly useful toward treatments of each of these contexts independently.

Comprehensive evaluation of the HIV specific repertoire remains a tremendous challenge due to the intra- and inter-infection diversity of the HIV genome. Typically, assays are limited to the response to a single reference strain, which may not be true to *in vivo* biology. However, strong and diverse responses to Gag have been affiliated with lower viral load, regardless of HLA background and mutation load[115,116]. Furthermore, modeling regions of Gag targeted by controllers versus progressors revealed structural biases indicative of mutational constraints[117]. Crystallographic analysis of the regions targeted by controllers also revealed a preference toward targets in interconnected regions of the protein[118]. Not only were mutations in these regions shown to impair viral fitness in general, but $CD8^+$ T cells targeting these regions in elite controllers tended to target regions less mutated at TCR contact sites and MHC anchor residues. Cross-reactive, or promiscuous, public TCRs have also been associated with HIV control in an HLA-dependent manner[119–122]. Although cross-reactive TCRs alone do not discriminate progressors from non-progressors, these results further suggest certain repertoire characteristics may be favorable in some contexts. While it may not be a strict rule, certain HLA backgrounds may pre-dispose an individual to producing TCRs that target favorable regions of the HIV proteome and/or resist immune escape through TCR promiscuity. It is possible that TCR-intrinsic properties influence the functional outcomes shown to be indicative of viral control. For instance, persistent antigen exposure has been shown to lead to exhaustion in both chronic infection and cancer[123]. If HIV control leads to more “normal” antigen exposure *in vivo*, CD8+ T cells from non-progressors may be more inclined to take on functional memory, non-exhausted phenotypes that bear a greater potential to continue to control the virus. This phenomenon has been demonstrated to some degree in a small, high-risk cohort, the magnitude of the $CD8^+$ T cell response was shown to correlate inversely with viremia in the early, hyperacute phase of HIV infection[124]. It is also possible that mutations on T cell targets may alter the quality of the TCR:pMHC contact, further leading to dysfunctional TCR signaling as has been seen in cancer models[125].

Pathogenic-derived antigens in neurodegeneration

Recent studies have demonstrated that T cell infiltration and clonal expansion is enhanced in neurodegenerative disorders such as AD[126–130], PD[131–135], ALS[136,137], and MS[138–141]. Although some of these disorders have T cell antigens that are more clearly defined such as in MS and PD, there is still a significant need for further investigating the antigenic source/breadth and the mechanisms in which they induce T cell activation.

While screening for T cell epitopes in pathogens is a well-defined task, screening for pathogen derived epitopes that mimic self-antigens is very challenging. Large scale epidemiological studies can often provide some clues. There is a growing body of evidence supporting the correlation between viral infections and cognitive disorders[142,143]. For example, AD pathogenesis has been associated with various viruses including herpes viruses, cytomegalovirus, HIV, Varicella zoster virus, EBV, and Hepatitis C[143,144]. Additionally, EBV infection is causally linked with MS as evidenced by an extensive longitudinal analysis of millions of US military personnel that were monitored for 20 years[80]. This study demonstrated that the risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses such as CMV. Out of the 801 MS cases, only one individual was EBV-negative in the last collected sample. Another study analyzed 148 BCR sequences which were found in the CSF of MS patients and demonstrated molecular mimicry between the EBV transcription factor EBV nuclear antigen 1, EBNA1, and the CNS glial cell adhesion protein, GlialCAM[81,145]. Specifically, this group identified a monoclonal antibody clone that binds the MS-associated EBNA1 region, $EBNA1_{AA386–405}$, which was then discovered to bind GlialCAM protein and phosphorylated peptide (pSer376 & pSer377) $GlialCAM_{AA370–389}$ with high-affinity. The presence of EBV-infected memory B cells has various implications on the pathophysiology of MS and may impact how aberrantly activated disease-relevant or bystander T cells contribute the initiation or relapsing of disease[146].

Using various T cell profiling strategies, Gate et al identified clonally expanded T_{EMRA} ($CD3^+CD8^+CD45RA^+CD27^-CD28^-$) cells enriched in the peripheral blood and CSF of patients with Alzheimer's disease and mild cognitive impairment[126]. The group identified a TCRαβ clone within the CSF of a patient with MCI and AD with previously identified specificity to the *Herpesviridae* Epstein–Barr nuclear antigen 3 (EBNA3A, FLRGRAYGL). They further identified a TCR clone that had shared beta chain homology found between three AD patients (2 patients: CASSLAGGYNEQFF, 1 patient: CASSLGTGNNEQFF). They validated that the TCR found in the single patient (TCRα: CAASEGGFKTIF; TCRβ: CASSLGTGNNEQFF) was able to recognize the EBV trans-activator protein BZLF1 (RAKFKQLL) presented on HLA-B*08:01, while the specificity of the other TCR clone was undetermined due to the limited screen of 80 candidate peptides that was performed. As the authors note, this finding does not provide evidence of a causal link between EBV and AD but does suggest that T cells recognizing both self and non-self-antigens should be evaluated when investigating the contribution of T cells in neurodegeneration.

The Arlehamn and Sette groups evaluated T cell responses to common pathogenic antigens in both PD and AD compared to healthy controls but did not find significant differences

using activation induced marker and peptide stimulation assays[127,147]. In their PD cohort, they evaluated T cells response to over 3000 viral and bacterial antigens across coronavirus, rhinovirus, respiratory syncytial virus, influenza, cytomegalovirus, pertussis, and tetanus across 19 patient and 20 healthy control PBMC samples.

Self-derived antigens in neurodegeneration

Some self-antigen screens have been performed on individuals who have MS, PD, AD, and other neurodegenerative disorders, but many of those screens have relied on functional stimulation assays which prevent detection of unmanipulated antigen-specific populations. For example, Arlehamn et al explored how tau pathology could influence the T cell landscape in PD, especially since aggregates of α-synuclein/tau oligomers are present in some patients[148]. They screened epitopes derived from tau and phosphorylated tau against T cells from control and PD patients using peptide stimulation of PBMC and measured cytokine production via ELISPOT. They identified that autoreactive T cell responses to tau were present at similar levels between PD patients and healthy controls. Interestingly, they also found that T cells responded more vigorously to tau than the PD-specific α-synuclein peptide. In a subsequent study, this group evaluated the frequency of T cells specific to amyloid precursor protein, amyloid beta, tau, α-synuclein, and TDP-43 in patients with AD and age-matched healthy controls using a similar peptide pool stimulation approach[127]. Similarly, no significant differences of cytokine response were found between AD and control.

Therefore, in evaluating T cell responses to self-antigens in neurodegeneration, one cannot assume that central tolerance is complete. Likewise, another study by Sabatino Jr et al demonstrated that there are similar frequencies of myelin-specific T cells in MS and healthy control, but the myelin-specific T cells in MS exhibit a non-naïve, antigen-experienced phenotype[139]. The group surveyed the landscape of myelin-reactive T cells in the PBMC of MS patients across five validated epitopes and found similar frequencies of myelin-specific T cells in MS and healthy control. However, the antigen-specific T cells found in MS were non-naïve, expressed CD20, and were significantly reduced in patients treated with anti-CD20 mAb therapy, suggesting prior antigen experience. These studies suggest that it is not always sufficient to only identify the presence or frequency of autoreactive T cells, but to fully characterize their specificity, phenotype, and functional capacity thoroughly to be able to understand which features are most implicated in disease.

In PD, the presence of self-reactive T cells toward epitopes derived from the pathological protein α-synuclein has a much stronger implication. A series of studies conducted by Arlehamn and Sette identified that more pronounced cytokine production was evident in PD compared to healthy controls in response to stimulation with several antigenic regions of α-synuclein (Y39: $\alpha\text{-syn}_{31–45}$ GKTKEGVLYVGSKTK, $\alpha\text{-syn}_{32–46}$ KTKEGVLYVGSKTKE and phosphorylated S129: $\alpha\text{-syn}_{116–130}$ MPVDPDNEAYEMPSE, $\alpha\text{-syn}_{121–135}$ DNEAYEMPSEEGYQD, $\alpha\text{-syn}_{126–140}$ EMPSEEGYQDYEPEA)[131]. A longitudinal case study identified α-synuclein specific ($\alpha\text{-syn}_{61–75}$ EQVTNVGGAVVTGVT) T cells in the peripheral blood of a motor PD patient years prior to their diagnosis, with the magnitude of the response waning after diagnosis[132].

Recently, these groups evaluated the TCR repertoire of α-synuclein-specific T cells in six PD patients and found that the repertoire was as diverse as the repertoire to antigens derived from Pertussis[149]. No public α-synuclein TCR was identified across the patients, though the patients were not HLA matched.

Campisi et al discovered highly expanded and activated $CD8^+$ T_{EMRA} cells in the PBMC of patients with ALS-4 and in the spinal cord, brain, and PBMC of mice with the ALS4-causative Senataxin L389S mutation[136]. Interestingly, these mice were able to control an induced high-grade glioma with high levels of activated CD8+ T cell infiltration, but not melanoma, suggesting an immune response directed against self-antigens of CNS origin. The clonal T cell sequences were also cross-referenced to known pathogenic antigens, and no overlapping sequences were identified. Additionally, control and ALS-4 PBMCs were stimulated with pools of self-peptide (TDP-43, Senataxin) or pathogen-derived peptides and IFNγ concentration was measured, but no difference between control and ALS-4 was identified. This result highlights the challenge of identifying and screening T cell antigens, even those which are strongly implicated in disease.

TCR cross-reactivities in neurodegeneration

Krishnamoorthy et al observed a paradoxical result in which spontaneous optic neuritis developed in TCR 2D2 MOG-deficient ($MOG^{-/-}$) transgenic mice which harbored TCRs specific to $MOG_{35–55}$ while $IgH^{MOG} \times MOG^{-/-}$ mice with B cells specific for MOG remained healthy[91]. They identified that the 2D2 transgenic T cells were cross-reactive to a neuronal cytoskeletal self-antigen, NF-$M_{18–30}$ which contained homology to the core residues of the $MOG_{35–55}$, but not to NF-$M_{225–237}$ (Table 1). Additionally, they determined that NF-$M_{18–30}$ can be targeted by polyclonal T cells isolated from $MOG_{35–55}$-specific T cells from C57BL/6 mice, indicating that this cross-reactive pair is not limited to a response by a single T cell clone.

In 1991, Brian Evavold and Paul Allen introduced altered peptide ligands (APLs) by demonstrating that the TCR can have differential signaling if its cognate epitope is conservatively altered with a single amino acid mutation[150]. A subsequent study by Dresseln et al aimed to evaluate the functional role of APLs in the context of peptides relevant in multiple sclerosis[151]. They screened ten variations of the peptide $PLP_{80–88}$ (FLYGALLLA), derived from myelin proteolipid protein for HLA-A2 binding along with cytotoxicity, cytokine secretion, and proliferative capacity against several T cell clones. Most of the ALPs had an HLA-A2 binding capacity (IC50) close to the wildtype (2.6 nM) with the exception of FL**A**GALLLA (599 nM) and FLY**A**ALLLA (17,177 nM). All altered peptides except FL**A**GALLLA were able to induce cytotoxicity by at least one of the $PLP_{80–88}$-specific T cell clones that were evaluated. Additionally, the L ➔ A mutation in position 87, FLYGALL**A**A, was able to act as a superagonist capable of inducing half-maximal cytotoxic, cytokine, and proliferative response with 100-fold less concentration compared to the wildtype.

APLs which compete for TCR binding but do not lead to full cellular activation have demonstrated efficacy in treating and reversing EAE through their capacity to

induce a T_H1 to T_H2 phenotype switch in myelin-specific T cells[152]. However, in clinical trials, this approach has faced significant challenges and has highlighted the complexity of the T cell response. A large double-blind phase II trial led by Neurocrine Biosciences evaluated an APL designed from the immunodominant myelin basic protein epitope, $MBP_{83–99}$ (NBI-5788), consisting of the following substitutions: D-Ala83-Lys84-Leu89-Ala91 (ENPVVHFFKNIVTPRTP ➔ AKPVVHLFANIVTPRTP). The APL was administered at various doses, and although there was no difference of the relapse rate between the APL and placebo group, there were smaller and fewer lesions in patients which received the lowest dose. However, the trial was suspended due to 13/142 patients developing immediate-type hypersensitivity and generating anti-NBI-5788 antibodies which could cross-react with the native peptide[152–154]. A smaller trial which included only eight patients evaluated the same APL at the higher dose level reported a strongly immunogenic response that led to the expansion of cross-reactive T cells for the APL and native protein. These trials suggest that although an APL may be capable of inducing anergy or an anti-inflammatory phenotype switch in some T cell clones, it could lead to activation of other clonotypes[152,153,155].

Cancer antigens

Leveraging the T cell ability to specifically recognize and destroy cancer is fundamental to the study of cancer immunology and the future progress of cancer immunotherapy. Cancer antigens can be categorized into two groups, tumor associated antigens (TAAs) and tumor specific antigens. Tumor associated antigens are not specific to tumors. They are expressed in healthy tissue but with an elevated expression in the tumor. For example, the first human tumor antigen identified to be recognized by T cells, mucin[156], is widely expressed on many types of cancers. Due to a lack of expression in healthy cells, tumor specific antigens provide great on-target specificity with minimum side effects. Tumor specific antigens can be categorized into four subclasses. Cancer testis antigens (CTA), also known as cancer germline antigens, are expressed in the embryonic stage and testis tissue but are epigenetically silenced in adult peripheral tissues. Because their expression at both RNA and protein levels have been detected in many types of cancers[157,158], these antigens are valuable candidate for cancer immunotherapy. However, not all CTAs are the same. In a recent clinical trial, autologous TCRs recognizing a shared epitope by several CTAs, MAGE-A3/A9/A12, caused severe neurological toxicity because unexpected expression of MAGE-A12 in human brains[159], highlighting the importance of selecting CTAs and understanding their individual tissue expression level for immunotherapy. The second class of tumor specific antigens is neo-antigens. Neo-antigens are mutated variants of self-proteins that are exclusively expressed by tumor cells (extensively reviewed in refs[160–164]). Depending on the self-proteins, neo-antigens can also be categorized as driver mutation-derived neo-antigens that are shared among different types of cancers or patient private mutations derived neo-antigens that are personalized to each patient. The third class of tumor specific antigens are antigens generated from non-protein-coding regions of DNA that are often called cryptic antigens. One example are peptides derived from alternative splicing or intronic retention or other post-transcriptional events[165]. The fourth class of tumor specific antigens are viral antigens expressed by cancers resulted from

viral infections, such as hepatitis B and C viral antigens in hepatitis B- and C-related hepatocellular carcinomas and human papillomavirus in cervical cancer. In addition to their unique tumor expression profile, neo-antigens and viral antigens are truly foreign that should retain high affinity TCRs from the thymic selection process[166].

Cancer antigen specific T cells

Initial cancer antigen specific T cell identification efforts primarily used limiting dilution analysis[167]. Using *in vitro* culture and cytotoxicity assays on autologous tumor cells, it has been shown that tumor reactive T cells can be identified[168]. Using TCR V region antibodies, it was possible to track antigen specific T cell repertoire[169] and measure their clonal size dynamics[170] and phenotypes[171] through vaccination. By combining flow cytometry sorting and PCR, analyzing TCR gene usage[172] was made possible for a polyclonal population of T cells responding to mouse syngeneic tumor cells transfected with a model peptide. A breakthrough came when John Alterman, Mark Davis, and colleagues developed pMHC tetramers[173] which can overcome the fast off-rate of low-affinity TCR-pMHC interactions. Using pMHC tetramers made with the TAAs MART-1, gp100, and tyrosinase peptides for melanoma[174] and PR1 for myeloid leukemia[175], they showed that functional tumor specific T cells can be isolated from CD8 T cell lines generated from healthy donors' PBMCs which could be exempt from the exhaustion program in the tumor microenvironment. Around the same time, using TAAs in melanoma, Labarriere et al[176], and Romero et al[177], independently identified tumor antigen specific T cells in metastatic lymph nodes of melanoma patients. Lee et al even analyzed the cytotoxicity of the T cells isolated from melanoma patients' PBMCs[178] and showed that they were functionally unresponsive compared with EBV or CMV specific T cells analyzed *ex vivo*. This is the first time that tumor antigen-specific T cell phenotype and function could be analyzed in their "native" state without prior stimulation.

Many studies have focused on neo-antigens because they are uniquely expressed in cancer tissue. This property enhances the on-target specificity of neo-antigen specific T cells while reducing the off-target toxicity. Since the discovery of the first T cell cognate neo-antigens in mice[179] and humans[180], large scale neo-antigen discovery have been aided by the development of next-generation sequencing (NGS) technologies and their applications in analyzing cancer genomes[181–183]. However, the discovery of neo-antigen specific T cells in those early days was only attainable for a few patients and was largely dependent on the ability to successfully generate *in vitro* T cell clones[161]. Robbins et al demonstrated for the first time that a patient autologous tumor infiltrating lymphocyte (TIL) derived T cell clone was able to recognize a neo-antigen[184]. The first attempt to exhaustively look for neo-antigens and autologous cognate T cells was done by Lennerz et al[185] prior to the development of NGS. Using a cDNA expression screen method, they discovered five neo-antigens and cognate T cell clones from the patient's peripheral blood in addition to three cancer associated antigens. This study demonstrated that the immune system has the capacity to target multiple cancer antigens, including multiple neo-antigens.

Aided by a peptide exchange method to quickly generate new pMHC species[186,187], Newell et al[188] and Hadrup et al[189] independently developed a combinatorial method to increase

the number of pMHCs that can be paralleled in the analysis. Using this method, Hadrup et al performed a screen of 22 pMHCs, derived from four melanoma associated antigens, in PMBCs from 28 HLA matched melanoma patients. A total of 24 T cell responses targeting eight epitopes were detected, five of which are previously unknown T cell epitopes. Further increases of the number of pMHC tetramer species that can be multiplexed arrived when the mass cytometry technology[190] became available. Subsequently, Newell et al combined mass cytometry with combinatorial tetramer stain and significantly expanded the number of multiplexed pMHC tetramers to over a hundred[191]. This technology opened the possibility of predicting and screening a large number of new T cell epitopes. Using mass cytometry, Simoni et al[192] screened 1091 putative neoantigens, 123 TAAs, and 46 cancer-unrelated epitopes in TILs derived from 24 patients with various types of cancers. Cognate TILs were detected for neoantigen epitopes but not any of the TAAs screened. Unexpectedly, they discovered a large population of common viral epitope specific TILs. These bystander CD8+ TILs lack CD39 expression compared to tumor antigen specific TILs, suggesting that tumor antigen specific TILs may have a distinct phenotype that could be further leveraged for their identification. Independently, Duhen et al[193] showed that co-expression of CD39+ and CD103+ identifies tumor-reactive CD8+ TILs in six different types of cancers, suggesting the value of focusing on a subset of TILs for prognosis during immunotherapy and identifying tumor antigen-specific T cells. Similar to Simoni et al[192], Scheper et al[194] also found that only about 10% of CD8+ TILs recognize autologous tumor. Therefore, the antigen landscape of TILs must be much more complex. Understanding the complexity of antigen specific T cells in tumor microenvironment could motivate new therapeutic development.

In addition to identifying bystander viral specific T cells in the TILs, Rosato et al[195] showed that injecting viral peptides into mouse tumors triggered antigen presentation and cytotoxicity in the tumor and, most strikingly, rendered PD-L1 blockade resistant mouse tumors susceptible to the treatment. Viral peptide-treated *ex vivo* human tumors recapitulated immune activation gene profiles observed in mice. Similarly, virus specific CD8+ T cells also populate mouse and human glioblastomas, which are one of the most aggressive and treatment-resistant cancers[196]. Thus, these studies suggest that intratumoral delivery of viral peptide triggers local immune activation and activating viral bystander cells in TILs represents an alternative or complementary approach to tumor antigen specific TIL activation in cancer immunotherapy.

With single cell RNA sequencing (scRNA-seq) becoming more accessible, it is possible to use TCR sequences as T cell IDs to link transcriptome data acquired directly from TILs to antigen specificity acquired from *ex vivo* expanded TILs. Oliveira et al[197] applied this strategy on a cohort of melanoma patients that received either neo-antigen vaccine or immune checkpoint blockade therapies. In addition to neo-antigen and common viral antigen specific TILs, they discovered TAA specific TILs. Non-tumor-reactive T cells exhibited a non-exhausted memory phenotype, whereas both TAA and neo-antigen reactive TILs displayed an exhausted state. Using a similar approach, Caushi et al[198] examined the clonality and activation status of neo-antigen and viral-antigen specific TILs and in a cohort of non-small cell lung cancer patients that received anti-PD-1 treatment before tumor resection surgery. Similar to the other two studies[192,197], neo-antigen specific TILs exhibited

an incompletely activated cytolytic program. Although neo-antigen specific T cells were found in both anti-PD-1 responders and non-responders, the ones found in non-responders showed lower ligand-dependent signaling, coordinately upregulated checkpoints, and other features that inhibit T cell activation. In a separate study, Lowery et al[199] used 55 TCR sequences from previously generated neo-antigen reactive T cell clones to track T cells in scRNA-seq data generated using archives of metastatic tumor samples. Using these signature TCRs, they were able to identify a subset of T cells that enriched with neo-antigen specific TCR. This allowed them to focus on a much smaller set of candidate TCRs and validate the neo-antigen targets in half of the predicted TCRs. These two studies opened the possibility of using neo-antigen specific T cell associated transcriptional program to track responses and predict new neo-antigen targeting TCRs. While this approach has been pursued mainly in cancer, possibly because of the unique transcriptional program of the tumor infiltrating T cells, it may be valuable to apply it to infection and neurodegenerative diseases. Recently, Puig-Saus et al[200] performed the largest neo-antigen specific T cell screen ever conducted for seven anti-PD-1 responders and four non-responders using DNA-barcoded pMHC multimers[201–203] on PBMCs and TIL cultures. Although neo-antigen cognate T cells were detected from both responders and non-responders, the ones from responders have more clonal expansion and showed up in multiple samples collected at different timepoints compared to the ones from non-responders.

Most of these attempts to identify T cell cognate neo-antigens focused on tumor mutational burden high (TMB-H) cancers[204,205] with a hypothesis that TMB-H cancers will induce more neo-antigen recognition by T cells[163]. However, various attempts in different types of cancers, including the ones discussed above, showed that the T cell cognate neo-antigen discover rate remains low, about 0–4%. The healthy status of the TILs, bias introduced by *in vitro* expansion, and various cancer immune evasion mechanisms, including HLA loss-of-heterozygosity, disruption to antigen presentation, and repression of neoantigen expression[206], all contribute to this low discovery rate. Zamora et al[207] took a different approach and found that 86% of the neo-antigens and 68% of the neo-peptides (multiple peptides containing the same mutation) are recognized by patients' autologous CD8+ T cells in pediatric acute lymphoblastic leukemia (ALL) that is on the extremely low end of the TMB spectrum[163,205]. This study suggested that having a few mutations may allow the immune system to focus on its repertoire and other recourse to mount a better immune response. Different tumor types could give rise to this difference. In addition, this study suggested that there might be fundamental differences between how pediatric immune systems recognize antigens compared to that of adults, which should be interesting to test in adult ALL patients.

McGranahan et al[208] showed that in both non–small cell lung cancer and melanoma, sensitivity to PD-1 and CTLA-4 blockade treatment was enhanced in patients who had more neo-antigens present in all tumor cells compared to patients who had neo-antigens in only a fraction of tumor cells. Steven Rosenberg's group showed in a series of papers that hotspot driver mutation can be targeted in adoptive cell transfer (ACT) therapy[209]. However, targeting a single neo-antigen only induced short-term clinical benefits and the cancer eventually evaded the immune system by downregulating the neo-antigen presenting HLA allele[210]. In a later study, they showed that targeting multiple neo-antigens could

result in complete durable regression in metastatic breast cancer. These studies highlight the importance of understanding the neo-antigen expression heterogeneity in selecting treatment targets to overcome immune evasion.

In addition to their abundance in spontaneous cancers, viral peptide specific T cells are a major therapeutic target in virus-induced cancers. Combining mass scRNA-seq with the use of a large panel of viral antigens, TAAs, bystander epitopes, and neo-antigens, Cheng et al[211] examined the antigen specificities of hepatocellular carcinoma (HCC) TILs, revealing that hepatitis B virus specific T cells exhibited a resident memory phenotype and transcriptional program. These cells were clonally expanded but were PD-1^{lo}TOX^{lo} and not terminally exhausted. Patients with these cells infiltrating to tumor had a longer-term relapse-free survival. Similarly, Eberhardt et al[212] screened and tracked human papillomavirus specific T cells in head and neck squamous cell carcinoma (HNSCC). TCR tracking and scRNA-seq analyses suggested hypothetical differentiation trajectory from TCF-1^{+}PD-1^{+} stem-like subset to transitory to terminally differentiated cells. *In vitro* peptide stimulation also confirmed their proliferation and differentiation capacity. Although both studies focused on virus-induced cancers, different viral infections, tumor microenvironments, or both could give rise to different TIL subsets that inform different treatment options. While immune checkpoint blockade therapies had poor responses in HCC[213], they have gained FDA approval for recurrent/metastatic HNSCC[214,215]. Both studies identified additional viral peptides that could be leveraged in the design of preventive and therapeutic vaccines that could be used in conjunction with other therapies.

TCR cross-reactivities in cancer

Although TCRs can specifically recognize tumor antigens, their cross-reactivity to other antigens have caused severe problems. One such example is an affinity enhanced TCR to its original antigen, CTA MAGE-A3, that caused death of two patients in a clinical trial. The fatalities were later linked to MAGE-A3's cross-reactivity to a peptide derived from the muscle protein Titin[216,217]. This has motivated alternative ways to fine tune TCR affinity and validate them in pre-clinical models[218]. Recent biophysical studies showed that "catch bonds", initially discovered in selectins[50] and integrins[51] and thought unique to adhesion molecules[219], existed in TCRs[52]. Chao et al. showed that high-affinity TCRs, measured by the traditional surface plasmon resonance, are often cross-reactive to self-antigens, however, low-affinity TCRs often lack functional efficacy. They demonstrated that it is possible to engineer TCRs with a low affinity to cancer antigen but have a strong cytotoxicity if the TCRs have a catch bond property. These TCRs are enhanced with on-target cancer antigen recognition but without cross-reactivity to off-target self-antigens[53]. This study provides a new avenue for engineering antigen specific TCRs for therapeutic development that can be applied to many other fields, such as infections and neurodegenerative diseases.

Other studies have explored possibilities of neo-antigen cognate T cells cross-reacting with wildtype proteins. Zhang et al showed that this type of T cell is readily detected in healthy individuals by using a large number of DNA-barcoded pMHC tetramer[202]. They also showed that these cells can be functionally validated through *in vitro* stimulation. By combining comprehensive peptide single position permutation experiments with informatics

approach on a NY-ESO-1 peptide, Karapetyan et al[220] validated 7 out of 12 highly scored cross-reactive peptide predicted from human proteome, including one that was 7 amino acid changes from the original nonomer peptide. These studies highlighted the complexity that TCR-antigen interaction spaces are and the importance of understanding the fundamental rule about TCR-antigen recognition has on cancer immunotherapy.

Informatic T cell epitope prediction

Computational prediction of TCR specificity can have immense utility in furthering our understanding of systems immunology and would lead to breakthroughs in translational immunotherapies. Recent reviews thoroughly highlight the various in silico modeling approaches aimed at predicting peptide-MHC binding, cross-reactivity, immunogenicity, and TCR-pMHC interaction[221–226]. Despite recent advances in both high-throughput TCR-antigen discovery and machine learning approaches, there exist significant challenges that need to be addressed. The fundamental limitation in most of these computational approaches can be attributed to the lack of experimentally validated, publicly available TCR-antigen pairs[221,224]. In fact, 97% of TCR-antigen pairs are those which are of viral origin and TCRs specific to a set of 100 antigens make up about 70% of the currently existing data[221]. Additional limitations include the lack of paired alpha-beta chains, HLA bias, lack of true negative datasets, and binary representation of the data (binder vs. non-binder)[221,223,224].

Many groups are actively developing novel strategies to overcome these limitations. Gao et al. developed Pan-Peptide Meta Learning (PanPep)[227,228], a framework which combines concepts of meta-learning and the neural Turing machine to address the challenge of the long-tail distribution that is characteristic in TCR-epitope data. Their model is constructed for three levels of predictions based on the amount of known TCRs for a given peptide: none (zero-shot), few (few-shot), and majority. PanPep significantly outperformed existing tools in the zero-shot and few-shot predictions. However, PanPep only considers the CDR3b chain and does not consider other relevant information such as alpha chain, HLA type, or 3D structure. Bradley[229] aimed to predict TCR-epitope interaction through structure-based analysis of the TCR:peptide-MHC complex by utilizing a custom version of the neural network predictor AlphaFold. Their pipeline, AlphaFold TCR, aims to select the correct target peptide from a small set of candidate peptides. This work provides a good proof-of-concept and highlights the utility in incorporating structure-based information in TCR-epitope predictions. Other groups are evaluating novel ways of the initial embedding of the TCR sequence to numeric representations. Zhang et al. propose catELMo[230], a bi-directional context-aware amino acid embedding model that treats amino acids as words and sequences as sentences. They demonstrate that their embedding approach can outperform other widely used approaches such as BLOSUM62 and BERT-based embedding models. Other groups are focused on gathering large datasets or generating databases to have more robust and easy-to-access training sets. Zhou et al. constructed NeoTCR[231], an immunoinformatic database consisting of publicly available neoantigen-specific TCR sequences across 18 cancer subtypes. This further highlights the need for a unified, well-annotated, and reliable TCR-epitope database.

Concluding remarks

The complex landscape of T cell and antigen interactions are critical to disease initiation and pathogenesis as well as diagnosis and therapeutic development. Because of the enormous impact both scientifically and therapeutically, waves of technological developments have advanced the field significantly in the last 30 years. Recent innovations make the exploration of the intricate interactions in the mesh network of TCR and antigen repertoires possible. Accompanying this is the exponential increase of high-dimensional data that link TCR-antigen interactions with T cell states. With groundbreaking computational tools that could enable the prediction of TCR antigen specificity and novel approaches for TCR engineering, the future of antigen-specific TCR-based disease diagnosis and therapeutics is incredibly bright. A deep understanding of the antigen specific immune response could unlock paradigm-shifting therapeutic potential, allowing us to harness its vast power for both protection from, and treatments against an immense array of diseases, from infections to neurodegenerative diseases to cancer.

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Table 1:

Select cross-reactivity examples. Epitopes derived from various antigens and their alignments are represented[58,61,86,89–91].

Epitope	Source	Sequences
B7/NP_{105}	SARS-CoV-2 HKU1, 0C43 (hCOVs)	SPRWYFYYL I I I I I I I I LPRWYFYYL
A24/S_{448}	WT (SARS-CoV-2) DELTA, BA.4/5	NYNYLYRLF I I I I I I I I NYNYRYRLF
B37/NP_{338}	H3N2 H1N1 pH1N1, H5N2. H7N9	FEDLELLSF I I I I I I I I FEDLRVLSF I I I I I I I I FEDLRVSSF
B35/$pp65_{123}$ B35/S_{1095}	CMV SARS-CoV-2	IPSINVHHY I I FVSNGTHWF
NF-$M_{18–30}$ $MOG_{35–55}$ NF-$M_{225–237}$	Mouse (self)	TETRSSFSRVSGS I I I I I I MEVGWYRSPFSRVVHLYRNG I I I I LQDEVAFLRSNHE