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BASEL, SEPTEMBER 8–11, 2022

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P1

Molecular characterization of BK polyomavirus replication in allogeneic hematopoietic cell transplantation

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Background: High-level BK polyomavirus (BKPyV) replication in allogeneic hematopoietic cell transplantation (HCT) marks failing immune control and BKPyV-associated hemorrhagic cystitis (BKPyV-HC).

Aim: To identify molecular correlates of BKPyV replication and BKPyV-HC.

Methods: We scrutinized BKPyV loads in 77 urines and 74 plasmas from 20 HCT patients using quantitative nucleic acid tests (QNAT), pre-extraction DNase-I digestion and next generation sequencing (NGS).

Results: We found that larger QNAT amplicons led to under-quantification and false-negatives ($p < 0.001$). DNase-I dramatically reduced urine and plasma BKPyV-loads by >90% ($p < 0.001$), indicating non-encapsidated BKPyV-genomes. DNase-resistant BKPyV-loads in urine remained infectious as expected for virions. BKPyV-genome fragmentation invalidated NGS-coverage of genetic variation using 1000bp and 5000bp targets. In contrast, 250bp-amplicons identified large T-antigen (LTag) and capsid Vp1 minority variants with frequencies <15%. This allowed identifying BKPyV genotype specific as well as genotype-independent changes in Vp1 or LTag, associated with escape from antibody neutralization or HLA-presentation to cytotoxic T-cells. Genotype-specific differences in LTag-encoded immunodominant 9mers were associated with reduced or absent CD8 T-cell responses. Thus, non-encapsidated, fragmented BKPyV-genomes reduce accuracy and precision of viral burden and sequence diversity.

Conclusion: Our results may prove to be important for patient management and immune protection through adoptive T-cell therapy and vaccine development.

P2

Successful desensitization to etoposide in a patient with a stade IV reaction

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Background: Etoposide is a chemotherapeutic agent, a podophyllin derivate, that inhibits mitosis and it's used as a treatment for malignant neoplasms. Hipersensitivity reactions to etoposide have been reported in 6 % of patients, while the incidence of anaphylaxis is 0.7 %. Different pediatric desensitization protocols have already been described, ranging from a six-step to a fifteen-step scheme, while adult published cases are scarce.

Aims: We present a case of a 61-year old woman with a small-cell lung cancer with brain metastases diagnosed in October 2019. In November 2019, she received the second cycle of cisplatine and etoposide. During the etoposide administration, she presented dyspnea and cardiorespiratory arrest, needing cardiopulmonary resuscitation and admission in the Intensive Care Unit.

Methods: The tryptase level during the reaction was 18 mcg/L (patient's basal tryptase level: 6,6 mcg/L). Skin testing with etoposide was not performed, given the severity of the reaction. Excipient hypersensitivity was excluded, given that after the reaction the patient tolerated Pembrolizumab (contains Polysorbate 80), metformin (contains macrogol 4000) and Irinotecan (contains sorbitol).

Results: We proposed a 16-step desensitization protocol to etoposide (total dose: 100 mg), which was well tolerated. However, etoposide dose had to be decreased due to hematotoxicity.

Conclusion: Desensitization protocol was therefore changed for a total dose of 50 mg (16 steps), and was successfully administered in two more cycles, until tumor progression that led to change of chemotherapy.

P3

Current epidemiology and features of Cryptococcus infection in patients without HIV infection: a multicentre study in 46 hospitals from Australia and New Zealand

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Objective: HIV-negative patients are increasingly being recognised as vulnerable to Cryptococcus. We conducted a multicentre retrospective study in Australia and New Zealand to describe the current epidemiology and features of cryptococcosis in HIV-negative patients, and to compare its frequency to that of HIV-associated cryptococcosis.

Methods: Forty-six hospitals from Australia and New Zealand participated. Adult patients who had cryptococcosis (defined using the 2020 EORTC/MSG definition) between 01/2015 and 12/2019 were included. Detailed data were collected using a standardized electronic data capture system.

Results: 475 patients had cryptococcosis during the study period. Around 90% of these cases occurred in HIV-negative patients (426/475 patients). Most HIV-negative cases were culture positive (312/426 cases [73.2%], including 228 due to C. neoformans, 82 due to C. gattii, and 2 due to other species. 259/426 HIV-negative patients (60.8%) had a known immunocompromising condition when cryptococcosis occurred (91 had cancer, 81 were organ transplant recipients, and 97 had another immunocompromising condition). Emerging group of patients were cancer patients receiving Bruton's tyrosine kinase inhibitors (12 cases) and multiple sclerosis patients receiving fingolimod (9 cases). Clinical, radiological and biological features are described.

Conclusion: In our study, around 90% of the cases of cryptococcosis occurred in HIV-negative patients. This rate, which was also observed when focusing on C. neoformans infections only, is much higher than in previously published large studies. This may be explained by factors such as the relatively low prevalence of HIV in our area, the widespread availability of highly active antiretroviral therapy to treat HIV, and the growing number of other immunocompromised patients.

P4

Tulip fingers – a rare occupational contact dermatitis to a common ornamental flower

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Introduction: "Tulip fingers" is an allergic contact dermatitis due to manual handling with tulip bulbs, which can occur as an occupational relevant dermatosis. We report a case of an impressive clinical presentation of tulip fingers with spreading eczema and discuss the diagnostics and management of this occupational disease.

Case report: A 29-year old woman who works as a gardener was referred to evaluate an eczematous eruption on the hands. She first reported developing eczematous skin lesions after contact with tulip bulbs. Under topical, moisturizing skin care as well as application of steroid cream, there had been a rapid recovery. During the next season in September 2020, she quickly developed an itch in the area of her hands just after a few days, even while applying protective measurements. After two weeks, she additionally developed a spreading exanthema on her face, neck, shoulders, elbows and trunk including swelling of the eyelids and lymphadenopathy while processing tulip bulbs. A patch test with the extract from the tulip bulb and Tulipaline A was positive clearly demonstrating a type IV-sensitization. Based on these findings the diagnosis of an allergic contact dermatitis to Tulipaline A could be underlined.

Conclusion: Tulip fingers can occur as an occupational disease due to a type IV-sensitization to tuliposide A. The diagnosis can be confirmed by epicutaneous testing. Protective measures are mandatory. The cornerstone of treatment lies in strict avoidance of the allergen. If this cannot be achieved, then occupational redeployment is recommended.

P5

Vaccine-elicited CD4 T cells prevent the deletion of antiviral B cells in chronic infection

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Background: Chronic viral infections subvert protective B cell immunity. An early type I interferon (IFN-I)-driven bias to short-lived plasmablast differentiation leads to clonal deletion, so-called "decimation," of antiviral memory B cells.

Aim: Prophylactic countermeasures against B cell decimation remain an unmet need for virus control.

Methods: Decimation of adoptively transferred B cells was studied in mice with chronic lymphocytic choriomeningitis virus (LCMV) infection.

Results: We show that vaccination-induced CD4 T cells prevented the decimation of naïve and memory B cells in chronically LCMV-infected mice. Although these B cell responses were largely T independent when IFN-I was blocked, preexisting T help assured their sustainability under conditions of IFN-I-driven inflammation by instructing a germinal center B cell transcriptional program. Prevention of decimation depended on T cell-intrinsic Bcl6 and Tfh progeny formation. Antigen presentation by B cells, interactions with antigen-specific T helper cells, and costimulation by CD40 and ICOS were also required. Importantly, B cell-mediated virus control averted Th1-driven immunopathology in LCMV-challenged animals with preexisting CD4 T cell immunity.

Conclusion: Our findings show that vaccination-induced Tfh cells represent a cornerstone of effective B cell immunity to chronic virus challenge, pointing the way toward more effective B cell-based vaccination against persistent viral diseases.

P6

Exocrine gland-resident memory CD8+ T cells use mechanosensing for tissue surveillance

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Tissue-resident CD8+ T cells (TRM) constitutively scan peptide-major histocompatibility complexes (pMHC) in their organ of residence to intercept microbial spread. While chemokines and integrin ligands produced at epithelial barriers are critical mediators of this process, their elevated constitutive expression in uninfected non-barrier organs might lead to excessive influx of immune cells. We recently found that exocrine gland TRM are programmed for autonomous tissue scanning in the absence of any chemoattractant or adhesion receptor engagement. The signals eliciting this non-canonical motility mode and its relevance for organ surveillance have remained unknown. Here, we report that exocrine gland TRM autonomously generated retrograde F-actin flow for locomotion, accompanied by high myosin IIA-dependent cortical contractility and leading edge bleb formation. The distinctive mode of exocrine gland TRM locomotion was triggered by sensing physical parameters of its microenvironment. Pharmacological blockade of mechanosensensing mediated by nuclear deformation and resultant arachidonic acid and Ca2+-signaling pathways, disrupted autonomous motility of exocrine gland TRM. In contrast, motility of naïve CD8+ T cells and small intestine TRM remained unaffected by the same treatment. In sum, mechanosensing of physical confinement suffices to elicit homeostatic T cell surveillance of exocrine glands, and acts to complement chemosensing-mediated migration in non-inflamed organs.

P7

DNA ligase 4 haploinsufficiency underlies autosomal dominant familial autoimmunity and immunodeficiency

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Background: Homozygous and compound heterozygous mutations in *LIG4* encoding DNA-ligase 4 cause a rare immunodeficiency syndrome manifesting as infant-onset life-threatening and/or opportunistic infections, skeletal malformations, radiosensitivity and neoplasia. LIG4 is pivotal during DNA repair and during V(D)J recombination as it performs the final DNA-break sealing step.

Purpose: Our aim was to explore whether *LIG4*-haploinsufficiency may underlie autosomal dominantly inherited autoimmunity.

Methods: Genetic analysis included whole-exome sequencing. DNA repair functionality was tested with *in vitro* and *in silico* tools. High-throughput sequencing allowed to characterise antigen-receptor diversity and autoimmune features.

Results: We describe a novel heterozygous *LIG4* loss-of-function mutation (c.G1739A; pR580Q), associated with a dominantly inherited familial immune-dysregulation consisting of autoimmune cytopenias, and in the index patient with lymphoproliferation, agammaglobulinemia and adaptive immune cell infiltration into nonlymphoid organs. Heterozygous *LIG4* mutated T cells displayed reduced DNA repair capacity and increased susceptibility to genotoxic stress. Alterations in T_{reg} phenotype and function as well as altered autoantibody profiles were found in *LIG4* mutation carriers, while T and B cell receptor repertoires showed only mild alterations.

Conclusions: These results suggest *LIG4*-haploinsufficiency as a cause of life-threatening immune dysregulation and widen the phenotypic spectrum of the disease manifestations associated with human DNA *LIG4* mutations.

P8

Treatment of anti-interferon-gamma autoantibody associated acquired immunodeficiency syndrome with bortezomib: pilot study

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Background: Currently there is no specific treatment for adult-onset immunodeficiency syndrome (AOIS) due to anti-interferon-gamma autoantibodies (anti-IFN-ϒ-auto-Abs).

Purpose: To determine the effectiveness of bortezomib (BTZ) in decreasing level of anti-IFN-ϒ-auto-Abs.

Methods: A pilot pre-and postintervention study was conducted between February 2017 and June 2019 at Siriraj Hospital, Bangkok, Thailand. Five patients with high titer of anti-IFN-ϒ-auto-Abs were invited to receive once weekly BTZ at the dose of 1.3 mg/m2 body surface area for 8 weeks and cyclophosphamide at the dose of 1 mg/kg/day for 4 months. The primary outcome was the difference of Abs level at 8 and 48 weeks compared to baseline. The clinical characteristics, opportunistic infections (OIs) and adverse event occurred within 72 weeks of enrollment were collected.

Results: Among 5 patients who were enrolled, the median age was 46 years (34-53 years) and 2 patients were male. All patients had 3-5 OIs before enrollment. There was no significant difference in the mean (**+**SD) optical density of auto-Abs at 8 weeks (3.73**+**0.72) and 48 weeks (3.74**+**0.53) compared to baseline (3.84**+**0.49) (p = 0.336 and p = 0.555, respectively). No recurrence infection was observed within 6 months of BTZ but 10 recurrent OIs were observed thereafter of which *Mycobacterium abscessus* and *Talaromyces marneffei* were found the most frequent.

Conclusions: Bortezomib was unable to reduce anti-IFN-ϒ-auto-Abs level in patients with AOIS. Recurrent infection occurred rarely during the first 6 months of BTZ but were observed thereafter.

P9

BCG (Bacillus Calmette-Guerin) septicemia in bladder cancer patient receiving intravesical BCG; cancer therapy caused uncommon infection

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Background: BCG was uncommon of human infection but reported in pediatric as post-BCG immunization infection & 1/15,000 of patients with bladder cancer received intravesical (IVC) BCG. BCG infection was difficult to differentiate from IVC BCG side effects or bacterial urosepsis.

Clinical case: An 83-year old man was diagnosed of bladder cancer, stage T1N0M0. 6 weekly treatments of IVC BCG treatment were prescribed. Patient was well tolerated with 1st-5thIVC BCG. At 6thIVC BCG, patient developed chill & rigor. Physical examination revealed T 36ºC & no other specific signs of infection. Urinary analysis showed wbc200, rbc 50, and few bacteria/hpf. Complete blood count showed hematocrit 36%, wbc 10,400/µL (neutrophil 93%). Meropenem was prescribed for empirical urosepsis therapy. Urine & blood culture were reported on Day-7 with molecular identification of *M.TB* complex which consists of 10 Mycobacterial species including *M.TB* & *M.bovis* & BCG strain. We communicated with microbiologist for suspected BCG infection; molecular identification for the mycobacterial species was done. Final culture reports were *M.bovis* BCG. Patient was treated with isoniazid, rifampicin, pyrazinamide & ethambutol for 2 months then H&R for 7 months.

Discussion and conclusion: We reported proven positive hemoculture BCG septicemia, a rare infectious complication of IVC BCG. Published case report & review was available but rare. Communication between physician and microbiologist is the key of success which is necessary since *M.TB* complex will be reported without species identification in adults.

P10

Cytokine complexes to boost perforin-independent cytotoxicity

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Background: The *in vivo* biological activity of cytokines can be significantly increased by complexing with anti-cytokine monoclonal antibodies. Furthermore, some cytokine complexes (cx) containing interleukin-2 (IL-2cx), can selectively stimulate effector cells such as Natural Killer cells and cytotoxic T lymphocytes or regulatory T cells. In the setting of experimental hemophagocytic lymphohistiocytosis (HLH), it has been shown that treatment with certain IL-2cx may result in the premature death of perforin (Prf)-KO animals, despite restoring the relative lack in regulatory T cells, which occurs during HLH.

Hypothesis: We hypothesized that modulation of effector cells by specific IL-2cx, might promote Prf-independent killing or CD8 T cell exhaustion and be beneficial during HLH.

Methods: Mice were infected with LCMV and euthanized on day 9 or 15. High-parameter flow cytometry was applied to phenotype cells, RT-qPCR to quantify viral titer and bead-based immunoassays to measure cytokines.

Results: IL-2cx treated mice showed a reduction in spleen size. Blood values of white blood cells and hemoglobin improved in treated animals. CD8 T cell numbers in both infected WT and Prf-KO mice decreased under IL-2cx treatment. Lower viral loads were measured in treated WT and Prf-KO compared to untreated mice.

Conclusions: We have set the prerequisites to investigate the biological activity of IL-2cx and tested whether specific IL-2cx could skew the cytotoxic machinery improving immune homeostasis in experimental HLH.

P11

Donor-derived TIM-3 deficiency underlying post-transplant inflammatory bowel disease

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The immune system is regulated by immune checkpoint proteins like T cell immunoglobulin and mucin domain 3 (TIM-3). Germline loss-of-function mutations in TIM-3 were linked with systemic immune activation and subcutaneous T cell lymphoma. Non-germline genetically determined TIM-3 deficiency has not been described so far.

Saliva, blood and skin samples of an index patient were examined by whole exome sequencing and by TIM-3 targeted Sanger sequencing. Freshly isolated peripheral T cells of healthy donors and the patient were stimulated with PHA and IL-2 and TIM-3 expression was analyzed by flow cytometry. TIM-3 expression of the intestinal tract of the patient *vs.* controls was analyzed in situ by immune-histology.

A patient with severe Crohn's disease occurring following stem cell transplant was found to carry a heterozygous pathogenic I97M missense mutation in *HAVCR2* encoding TIM-3 in donor-derived hematopoietic but not in skin-derived cells. TIM-3 expression following *in vitro* stimulation of donor derived T cells was almost completely absent. Immune-histology of the intestinal tract of the patient revealed that TIM-3 expression was virtually absent in inflamed and in non-inflamed intestinal tract of the patient.

The patient had been engrafted with stem cells carrying a disease-causing mutation in TIM-3 causing nearly absent TIM-3 expression following activation *in vitro* but also in the intestinal tract *in vivo*. This is to our knowledge the first report of hematopoietic cell-restricted TIM-3 mutation/deficiency associated with severe post-transplant inflammatory bowel disease.

P12

Change for the better: severe pneumonia at the emergency department

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Pneumonia a common infection, causes significant morbidity and mortality and remains a challenge to the clinician at the Emergency Department, between 1 January 2019 and 15 October 2020: 398 patients with acute pneumonia were included. For each patient, information about demographics, mortality, and ED and hospital length of stay, clinical data, microbiological test results and radiological features was collected. The median age of patients was 73 years. Around 65% of patients had at least one chronic comorbidity. Almost 30% of patients had cardiovascular disorders, and 13% suffered from DM. The average ED length of stay 3.56 days (median: 1.88 days). The average length of hospitalization was 15.8 days (median: 12 days). The majority of patients (87.2%) received an antimicrobial agent during the ED stay. In the course of hospitalization, 94% of patients treated for pneumonia received a beta-lactam antibiotic.

Microbiology test samples were obtained from 48.7% patients (69.6% of samples were negative). In total, 51 microbial isolates were cultured from blood: true positive (27.3%). Gram-positive cocci (52.9%) were isolated most commonly, of which CNS (51.8%) made up the largest group. Biological material from the lower respiratory tract was collected from 8.3% of patients. The tracheal aspirate (60.6%) was collected most frequently. Pathogens were cultured from 75.7% respiratory tract samples, from 47.2% of samples fungi were cultured. Overall 16.1% of patients died during the hospitalization.

P13

Rezafungin treatment of candidemia and invasive candidiasis: outcomes stratified by baseline renal function – analysis of the phase 2 + phase 3 trials

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Background: Rezafungin (RZF) once weekly (QWk) is a next-generation echinocandin in development for treatment of candidemia and invasive candidiasis (IC) and prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp. in BMT. RZF QWk was compared to caspofungin (CAS) QD in two double-blind, randomized, controlled trials of treatment of candidemia and/or IC: STRIVE (Phase 2, NCT02734862) and ReSTORE (Phase 3, NCT03667690).

Aim: Trial data (Phase 2+Phase 3) were analyzed to evaluate outcomes stratified by renal function at baseline: CrCl ≥60 mL/min (normal/mild impairment [Norm/Mild]) and <60 mL/min (moderate/severe impairment [Mod/Sev]).

Methods: Outcomes were evaluated for differences between CrCl categories and between treatment groups: RZF QWk 400mg on Wk 1 then 200 mg vs CAS QD 70 mg on Day (D)1 then 50mg, for ≥14 days (≤4 wk) w/optional oral fluconazole stepdown for CAS.

Results

– D30 all-cause mortality (ACM)
  – Mod/Sev: RZF, 13% (7/54); CAS, 30.5% (18/59)
  – Norm/Mild: RZF, 22.7% (17/75); CAS, 10.8% (9/83)
– Mycological eradication (ME) at D5
  – Mod/Sev: RZF, 75.9% (41/54); CAS, 61.0% (36/59)
  – Norm/Mild: RZF, 74.7% (56/75); CAS, 66.3% (55/83)
– ME at D14
  – Mod/Sev: RZF, 75.9% (41/54); CAS, 57.6% (34/59)
  – Norm/Mild: RZF, 69.3% (52/75); CAS, 74.7% (62/83)
– ≥1 treatment-emergent AE
  – Mod/Sev: RZF, 93.2% (55/59); CAS, 88.9% (56/63)
  – Norm/Mild: RZF, 88.9% (72/81); CAS, 76.7% (69/90)

Conclusions: RZF efficacy was comparable across CrCl categories, with higher ME and lower D30 ACM in Mod/Sev group. Further analyses are needed to evaluate the observed differences between treatment groups.

P14

Multi-virus-specific T-cell bank to treat ADV, BKV, JCV, CMV and EBV infections in immunocompromised patients using a HLA-defined peptide platform

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Background and Aim: Opportunistic viral infections pose a significant threat among transplant recipients. Antiviral drugs show little to no effect in many patients; however, adoptive T-cell therapy has been shown to be beneficial against individual viruses. Hence, we aimed to develop a single off-the-shelf T-cell product which could be used to tackle multiple virus reactivations and disease progression in immunocompromised patients using a HLA-defined peptide platform.

Methods: GMP-compliant process was developed using individual peptide pools containing T-cell epitopes from CMV, EBV, BKV, JCV and EBV to expand multi-virus-specific T cells (MVT). Viral specificity, polyfunctionality and alloreactivity of the allogeneic T cells was assessed using flow cytometry.

Results and Conclusion: We have designed peptide pools with a HLA coverage of >95% for all five viruses and have successfully expanded 20 T-cell products with heterogeneous populations of $CD4^+$ and $CD8^+$ T cells. MVT products showed specificity and polyfunctionality against all five viruses and showed no alloreactivity. These third-party T cells were used to treat immunosuppressed patients with viral reactivations through Special Access Scheme. Early results have shown clinical improvements in patients with reactivation of BKV (7/8), CMV (2/3), EBV (1/1), ADV(2/2) and JCV (1/1). A phase I clinical trial is currently ongoing. In conclusion, we have successfully established an "off-the-shelf" multi-virus-specific T-cell bank using a HLA-defined peptide platform that provide safe and effective treatment of multiple viral complications in immunocompromised patients.

P15

Microbial triggering of myelin-specific immune cells in the gut drives central nervous system inflammation

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Background: Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS) of unknown etiology. It is a prototypic complex disease in which genetic and environmental factors are thought to lead to dysregulated immune responses targeting myelin antigens. In that regard, changes in gut microbiota composition have recently been implicated in MS pathogenesis.

Purpose: How alterations in gut microbiota composition influence systemic immune responses in an antigenic specific manner and

whether this interaction can trigger myelin-reactive immune responses in the gut through molecular mimicry with commensal bacteria in MS is unknown.

Methods: Here, we studied antigen-specific triggering of gut immune cells and their encephalitogenic potential in experimental models of autoimmune neuroinflammation.

Results: We found that myelin peptide-expressing – but not bacteria expressing ovalbumin – were capable of triggering or exacerbating disease in different experimental murine models of MS.

Conclusion: Our results provide novel insights into antigen-specific microbial triggers of MS with implications for the development of novel therapeutic strategies that aim at manipulating the MS gut microbiome.

P16

Characterization of BKPyV serotype-specific antibodies and T cell responses in kidney transplantation

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BK Polyomavirus (BKPyV) is a non-enveloped double-stranded DNA virus infecting >90% of the human population without ill effects, but causes nephropathy, hemorrhagic cystitis and urothelial cancer in transplant and other immunocompromised patients. BKPyV consists of 4 major serotypes defined by domains of the capsid protein Vp1. It has been reported that recipients with low or absent serotype-specific neutralizing antibodies against the donor virus serotype have higher risk of BKPyV-DNAemia/nephropathy. Moreover, we recently identified amino-acids exchange in immunodominant large tumor antigen (LTag)-specific CD8 T cell epitopes associated with certain serotypes. Serotype mismatches and serotype-associated mutations may contribute to the failure of immune control over BKPyV-replication after kidney transplantation.

To investigate serotype-specific humoral responses, we developed virus-like particles specific for each serotype and tested the presence of IgG in plasma samples of healthy donors (HDs) by ELISA. We demonstrated that some HDs have serotype-specific IgG antibodies which are not cross-reacting with other serotypes. To further assess serotype-specific cellular responses, we stimulated peripheral blood mononuclear cells with LTag-derived peptides harbouring specific mutations associated with serotypes and performed T cell functional assay detecting IFNy release.

These findings will guide us for the design of an efficient vaccine increasing the humoral and cellular BKPyV-specific immunity across major BKPyV-serotypes.

P17

Generating a Virus-Like Particles based vaccine against IgE

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IgE plays a significant role in type I allergy which is characterized by the induction of IgE responses towards harmless antigens. Cross-linking by allergens of IgE bound to its high-affinity receptor (FcεRI)-expressed on mast cells and basophils- leads to cellular activation, degranulation and releasing inflammatory mediators. As this receptor cross-linking plays a key role in initiating allergic reactions, we aimed at developing a vaccine targeting IgE antibodies by inducing a protective anti-IgE immune response which blocks IgE-FcεRI interaction. To get such a vaccine, we generated two IgE-Fc fragments (Cε2-Cε3-Cε4, Cε3-Cε4) and chemically coupled them to virus-like particles (VLPs) derived from cucumber-mosaic virus which contain an universal Tetanus toxoid epitope. The reason to choose Cε domains is that the entire IgE antibody is a large molecule and difficult to efficiently be coupled to VLPs. Additionally, IgE-Fc is the region responsible for its effector functions as the binding site for FcεRI receptor is located in Cε domains. To test the immunogenicity of the VLP-Cε vaccines, BALB/c mice were sensitized with allergen two weeks prior to immunization followed by assessing IgG anti-IgE response by ELISA and FluoroSpot. Our data showed high titer of anti-IgE antibodies plus detectable secreting plasma cells post immunization, moreover, downregulation of IgE levels in serum and on basophils. Consequently, suppressed systemic anaphylaxis upon allergen challenge indicates that the vaccines have the potential to use as a therapeutic method against IgE-mediated allergy.

P18

CMV reactivation and CMV-cell mediated immunity after chimeric antigen receptor (CAR)-T-cell immunotherapy for B-cell malignancies: a prospective study

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Background: The epidemiology of CMV reactivation after CAR-T-cell therapy (CARTx) is poorly understood due to lack of routine surveillance.

Aims: To assess the epidemiology of and risk factors for CMV reactivation after CARTx.

Methods: We prospectively enrolled CMV-seropositive adult CARTx recipients and obtained blood once pre- and weekly post-CARTx for up to 12 weeks for testing with quantitative CMV PCR. We tested CMV-specific T-cell responses to IE-1 and pp65 antigens using an IFN-γ release assay (T-SPOT®.*CMV*) to assess CMV cell-mediated immunity (CMI) pre- and at week 2 and 4 post-CARTx. We estimated the cumulative incidence of CMV reactivation and compared CMV-CMI between those who did and did not reactivate.

Results: We present data on the first 36 enrolled patients contributing a median follow up of 81 days (IQR: 28, 83). CMV was detected in 1 patient pre- and 7 patients post-CARTx with a cumulative incidence of 21% (95% CI: 7-34) after CARTx; two (6%) received preemptive therapy. The median viral load was 140 IU/mL (IQR: 57-276) and median time to first positive test was 21 days (IQR: 19-27). CMV reactivation was more frequent in patients receiving treatment for CRS or ICANS (5/14, 36%), and 5/7 (71%) patients with CMV detection had grade ≥2 CRS or ICANS. CMV-CMI values reached a nadir at week 2 post-CARTx and were numerically lower in patients with subsequent CMV reactivation.

Conclusions: CMV reactivation is frequent in CARTx recipients receiving immunosuppression for CRS or ICANS; CMV-CMI 2 weeks post-CARTx may identify high-risk individuals.

P19

Treatment with obinutuzumab leads to worse outcomes in hematological patients diagnosed with Omicron variant COVID-19

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Background: Hematological malignancies (HM) patients treated with anti-CD20s are at a higher risk for COVID-19 complications, however, little is known about the difference between these agents.

Aim: To investigate the prognosis of HM COVID-19 pateints treated with obinutuzumab in comparison to rituximab.

Methods: Single-center population-based cohort study including all HM patients treated with anti-CD20s from June 2021 to April 2022. Diagnosis of COVID-19 was based on positive SARS-CoV-2 PCR omicron variant. The Median follow-up was four months.

Results: Among 143 HM patients, 47 were diagnosed with COVID-19, 27 in the rituximab group and 20 in the obinutuzumab group. All obinutuzumab-treated patients had indolent HM, versus only 40.7% among the rituximab group ($p < 0.001$). 13/20 of the obinutuzumab group (65.0%) received anti-CD20s as maintenance therapy, while most of the rituximab patients, 21/27 (77.8%) were on induction

phase therapy (p = 0.003). COVID-19 prognosis was worse among obinutuzumab patients with higher admission rates (60.0% vs. 25.9%, p = 0.019), more patients with severe-critical disease (35.0% vs.7.4%, p = 0.017), and accounts for all mortality cases (3/20 vs. 0/27, p = 0.038).

Conclusions: Omicron-variant COVID-19 disease outcome was worse among HM patients treated with obinutuzumab comparing to rituximab. As this treatment has not been shown to increase overall survival when given as maintenance, In our opinion, it may be prudent to delay treatment with obinutuzumab or replace it with a less potent anti-CD20 as long as the COVID-19 epidemic continues.

P20

Method comparison between T-SPOT.CMV and QuantiFERON-CMV for immunological monitoring after allogeneic stem cell transplantation

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Background: CMV-reactivation and -disease is still a major concern after allogeneic stem cell transplantation [allo-HSCT], despite prophylactic and pre-emptive strategies. In recent years, immunologic monitoring using CMV-IGRA has gained interest to better risk stratify immunocompromised patients or to guide prophylactic therapies. In the setting of allo-HSCT, the two most widely used CMV-IGRAs, T-SPOT.CMV and QuantiFERON-CMV, have not yet been compared.

Aim: To perform a method comparison 28 and 100 days after allo-HSCT, and to assess predictive values of both tests for CMV-reactivation.

Methods: In a bicentric prospective trial, 27 patients were included. Samples were taken on day +28 and day +100 after allo-HSCT. Patients' clinical information was collected up to one year after transplant. Method comparison was performed using Cohen's kappa.

Results: Method comparison showed a strong agreement on day +28 (κ = 0,780), but only a moderate agreement on day +100 (κ = 0,578). However, both tests have a very high NPV and sensitivity of 100% for both on day +100 for clinically significant CMV-reactivation, but a lower PPV and specificity (T-SPOT.CMV 21,4% resp. 31,3%; QuantiFERON-CMV 25,0% resp. 43,8%).

Conclusions: The moderate agreement of both tests on day +100 is lower than could be expected and shows the need for a large validation study of the QuantiFERON-CMV in the setting of allo-HSCT. The high NPV and sensitivity is encouraging and corresponds with the results of other studies. It shows the promise of reliable CMV-specific immunological monitoring after allo-HSCT.

P21

Immune tolerance defects in individuals with pathogenic mutations in the kappa light chain

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Germline homozygous or compound heterozygous mutations in the gene encoding the constant domain of the immunoglobulin κ light chain (*IGKC*) may cause kappa light deficiency. Only few cases have been reported since its first characterisation, with very variable susceptibility to infections. κ light chain expression is involved in the process of B cell receptor (BCR) editing, a pivotal autoimmune checkpoint. Thus, *IGKC* mutations might predispose to autoimmunity.

We screened our inborn errors of immunity cohort consisting of 360 patients by Sanger sequencing for rare *IGKC* mutations. In addition, we screened 490 individuals of the Swiss SLE Cohort Study and 500 patients enrolled into a Swiss Rheumatoid Arthritis cohort. *IGKC* mutation carriers were characterised clinically. We comprehensively evaluated the immune-phenotype including κ vs λ light chain expression on B cell subpopulations by flow-cytometry.

So far, we have identified five individuals carrying the heterozygous c.T258G mutation in *IGKC*. This mutation changes an essential cysteine involved in disulphide bonds. Only one mutation carrier had kappa light chain deficiency in the serum. However, all expressed predominantly λ light chains on the surface of peripheral B cells implicating pathologic receptor editing. All mutation carriers had autoimmune disease, which in the majority was life-threatening.

We present evidence that the c.T258G *IGKC* missense variant in heterozygous state disturbs B cell receptor editing with high penetrance. The clinical associations found indicate a considerable penetrance of the c.T258G *IGKC* mutation to drive human autoimmune disease.

P22

Anti-chemokine antibodies after SARS-CoV-2 infection correlate with favorable disease course

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Infection by SARS-CoV-2 leads to diverse symptoms, which can persist for months beyond the acute phase of the disease. While antiviral antibodies are protective, the presence of antibodies against interferons and other immune factors is associated with adverse COVID-19 outcomes. Instead, we discovered that antibodies against specific chemokines are omnipresent after COVID-19, associated with favorable disease, and predictive of lack of long COVID symptoms at one year post infection. Autoantibody levels against some chemokines are sustained or even increasing over time. Anti-chemokine antibodies are present also in HIV-1 and autoimmune disorders, but they target different chemokines than those in COVID-19. Finally, monoclonal antibodies derived from COVID-19 convalescents that bind to the chemokine N-loop impair cell migration. Given the role of chemokines in orchestrating immune cell trafficking, naturally arising anti-chemokine antibodies that are associated with favorable COVID-19 may be beneficial through modulation of the inflammatory response and thus bear therapeutic potential.

P23

Engineered single amino acid substitutions protect therapeutic cells from CD123 targeted immunotherapy in vitro

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Background: Diseased cells can effectively be depleted using monoclonal antibodies, T cell engagers (TCE) or chimeric antigen receptor (CAR) cells. Whereas B cell targeted immunotherapies are highly specific, the co-expression of myeloid markers such as CD33 or CD123 on healthy hematopoietic stem and progenitor cells(HSPCs) bears the risk for unintentional myelotoxicity. In order to enable therapeutic targeting of such proteins it was proposed to transplant engineered HSCs in which the target was removed. However, since removing the protein abolishes its function, this approach is limited.

Aim(s), purpose or hypothesis: Here, we show feasibility for shielding the therapeutic cells from targeted therapy while preserving the function of the targeted receptor.

Methods and Results: Structure-guided computer modeling identified 28 single amino acid (aa) substitutions in CD123 (IL3 alpha

chain receptor) designed to interfere with CSL362 antibody binding but preserve CD123 function. Using flow cytometry of cells expressing the variants we identified variants for which the single aa substitution resulted in complete non-binding while CD123 remained normally expressed. Cells expressing non-binding variants were shielded from antibody dependent cellular cytotoxicity, TCE or CAR T-mediated killing. Moreover, preserved function of CD123 variants was shown in a genetically engineered IL3-dependent cell line using a proliferation assay.

Conclusions: Thus, our data demonstrates the feasibility to engineer proteins harboring single aa substitutions that shield therapeutic cells from all tested cell depleting modalities while preserving their function.

P24

Impact of time from transplant to treatment of patients with refractory cytomegalovirus infection: post hoc analysis of Phase 3 SOLTICE study

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Background: In this Phase 3 study (NCT02931539), maribavir (MBV) was superior to investigator-assigned therapy (IAT) for CMV viremia clearance at Study Wk 8 in HCT/SOT recipients with refractory CMV infection with/without resistance (R/R).

Aim: To explore if time from transplant to randomization impacted treatment (tx) efficacy with MBV or IAT (val/ganciclovir, foscarnet or cidofovir) in SOLSTICE.

Methods: Pts were randomized 2:1 to MBV or IAT for 8 wks, with 12 wks follow-up. The primary endpoint was confirmed CMV clearance at the end of Wk 8. This post hoc analysis evaluated the impact of time from transplant to randomization with time as a categorical variable or a continuous covariate (by month).

Results: There was no statistical difference between MBV and IAT tx arms in median time from transplant. By time categories, 64 and 28 (≤3 mo), 53 and 28 (3–6 mo), 62 and 39 (6–12 mo), and 55 and 21 (>12 mo) pts received MBV or IAT, respectively. More MBV-treated pts achieved confirmed CMV clearance at the end of Wk 8 than those treated with IAT in all time ranges explored (≤3 mo 50% vs 21%, 3–6 mo 68% vs 46%, 6–12 mo 57% vs 15%, >12 mo 51% vs 14%). Time from transplant had no effect on either CMV clearance at end of Wk 8 or recurrences requiring tx between Wks 8 and 20 when time was used as a continuous covariate.

Conclusions: In this post hoc analysis, higher proportions of pts treated with MBV achieved CMV clearance at end of Wk 8 than with IAT, irrespective of time from transplant to randomization.

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P25

Defining the translatome of HIV-1 to identify novel conserved T-cell antigens

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CTL recognize peptides derived from open-reading frames (ORF) encoding the classical viral proteins but also peptides encoded by alternative reading frames (ARF). ARF-specific CTL are elicited in the course of HIV-1 infection. These CTL responses exert a selective pressure on the virus and are preferentially detected in HIV+ patients expressing protective HLA alleles. However, we have an incomplete view of the repertoire of ARF in HIV-1 genome.

In our study, we defined the translatome of HIV-1 using Ribosome Profiling**.** This technic allows a systematic identification of ORF by direct isolation and sequencing of mRNA fragments protected by ribosomes during translation. In HIV-1 infected cells, we unravelled 98 HIV ARF among which 9 overlap the LTR region while the others are distributed across HIV genome. Using an in-house HIV-1 database we show that these ARF are highly conserved among HIV-1 clade B isolates.

Using two complementary approaches, we further show that at least 42 ARF encode viral polypeptides. To this end, we used cultured-IFNg Elipot assay to identify in PBMCs of patients T cells responses targeting ARF-derived peptides and immunopeptidomic approaches. Remarkably we also assess the quality of T cell responses targeting ARF and we show that the majority of these responses are mediated by CD4+ T cells and polyfunctional.

Our study highlights the immense coding capacity of the HIV-1 genome. We have defined the first complete map of translated HIV ORF and ARF. We unravelled new conserved viral polypeptides that are potential targets for vaccination strategies.

P26

Risk for infections and longitudinal antibody profiles in glucocorticoid treated large-vessel vasculitis

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Background: *Infections are frequent in immunosuppressed patients. Giant cell arteritis (GCA) is an autoinflammatory vasculitis treated with high-dose glucocorticoid (GC).*

Aim: *We assessed how GC treatment and adaptive immune factors related to the infection prevalence in GCA.*

Methods: *Characterization of infections in patients from a prospective observational cohort. Treatment information was extracted to calculate cumulative glucocorticoid doses. We assessed adaptive immunity by quantifying the total immunoglobulin* classes and pathogen-specific IgG (anti-tetanus toxoid and 14 serotype-specific anti-pneumococcal) at baseline and follow-up. Hierarchical clustering was performed to define patient subsets based on immunoglobulin levels.

Results: *In total, 85 infections occurred in 53/111 (48%) GCA patients. Community-acquired pneumonia (CAP) accounted for 20/30 severe infections. The infection rate was highest during the first six months of therapy. Treatment-induced hypogammaglobulinemia was frequent: 23% had IgG levels <5g/l after three months (*vs. *3% at baseline and 14% after 12 months). IgA, but not IgM, were also significantly reduced but remained normal. An unsupervised analysis detected three clusters based on relative IgG, IgA, and IgM baseline levels. An $IgG^{low}IgA^{high}IgM^{low}$ cluster defined a group with a 25% prevalence of CAP (vs. 8.6% and 9.1% in the other clusters). Seroprotection rates against tetanus and pneumococcal serotypes were 60% and 55%, respectively, at baseline and remained stable despite declining pathogen-specific IgG during treatment.*

Conclusion: *Infection, especially CAP, was a frequent complication in the first months of newly treated GCA. Combining total IgG, IgA, and IgM measurements* at baseline may help identify patients at the highest risk for CAP. Increasing the vaccination rate, reducing immunosuppression, or evaluating immunoglobulin replacement therapy are options to reduce infections in these high-risk patients.

P27

Enhanced anti-COVID immunity in subjects with strong local temperature reactions to mRNA vaccines

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Aim: Local vaccine reactogenicity results from the vaccine induced immune activation. Little is known how local reactogenicity affects the quality and quantity of the vaccine response. Here, we studied the factors contributing to local reactogenicity to the mRNA COVID vaccination and the immunological consequences of a strong inflammatory local reaction.

Methods: We studied 42 healthy subjects receiving a second dose of the mRNA-1273 COVID vaccine (Moderrna®). Local temperature reaction was measured at the vaccination site before and after 24h vaccination. We performed immunophenotypic analyses, measured cytokines, and quantified anti-Spike-antibodies including their neutralization capacity. Vaccine-induced spike protein production in monocytes was assessed i*n vitro*.

Results: The median local temperature increase after vaccination [DT(vaccinated arm – control arm) was +1.45 °C. A strong temperature reaction (³1°C) was associated with increased pro-inflammatory cytokines. Temperature increase was not correlated with the levels of anti-Spike-IgG (r = 0.42) but with virus neutralization (r = 0.71). T cell responses to the spike protein, and *in vitro* vaccine-induced monocyte activation and spike production were enhanced in subjects with stronger local thermic reactions.

Conclusions: Strong thermic reactions associate with a more robust vaccine response, including T cell responses and neutralizing antibodies. The role of enhanced vaccine antigen production in subjects with strong thermic reactions needs to be further defined.

P28

Impact of SARS-CoV-2 RNAemia on prognosis of immunocompetent adults and solid organ transplant recipients with COVID-19

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Background: The COVID-19 pandemic remains a large contributor to the global burden of disease. SARS-CoV-2 RNAemia detection has been connected to higher mortality, but consistent data of solid organ transplant (SOT) recipients have not been analyzed.

Aim: To determine and quantify RNAemia at hospital admission and its impact on robust unfavorable clinical outcomes.

Methods: From January 6, 2020 to August 13, 2021, we followed a multicenter cohort of 408 immunocompetent and 47 SOT patients hospitalized with COVID-19. Outcome variables were 30-day all-cause mortality and invasive mechanical ventilation. Multivariate Cox regression analyses were performed and a propensity score (PS) was calculated.

Results: SARS-CoV-2 RNAemia was demonstrated in 104 (22.9%) patients. Those with RNAemia were more frequently transplanted and presented a higher proportion of severe symptoms and signs. Mortality was 29.8% (31/104) and 3.4% (12/351) in RNAemic and non-RNAemic patients (p <0.001). The multivariate analysis adjusted by PS selected CURB-65≥2 (HR, 3.61; 95% CI, 1.18–11.01; p = 0.02) and RNAemia (HR, 7.46; 95% CI, 2.41–25.38; p = 0.001) as independent predictors of death. In the PS matching, SOT patients showed higher prevalence of RNAemia (57.6% *vs.* 13.6%) and mortality (HR, 4.56; 95% CI, 1.47–7.13; p = 0.01).

Conclusions: Positive RNAemia is an independent predictor of unfavorable outcome in immunocompetent and SOT. High viral load was linked to worse prognosis in a univariate analysis. Our findings help elucidate the pathogenesis of SARS-CoV-2 and provide insights for the better management of patients.

P29

Hospital onset SARS CoV-2 infections before and after the emergence of the highly transmissible variant B.1.1.529 in a comprehensive cancer center

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SARS-CoV-2 B.1.1.529 (Omicron) variant was first identified in November 2021 and was notable for its transmissibility and rapid spread worldwide. Here, we compared the incidence and characteristics of hospital-onset COVID-19 (HO-COVID-19) in our cancer patients prior to and during the surge of the Omicron variant.

Following CDC definitions, we identified HO-COVID-19 from our infection control surveillance database. Whole-genome sequencing studies were conducted randomly on positive nasopharyngeal swabs during the study period.

Twenty-six HO-COVID-19 infections were identified from February 2020 through February 2022. Only 17 cases occurred over 22 months from the beginning of the pandemic through early December 2021. These HO-COVID-19 occurred during the 3 COVID-19 surges that were epidemiologically attributed to the variants seen prior to Omicron. Among these 17 patients, 12 (70%) were symptomatic, 9 (53%) had a link to an infected employee, 7 (41%) died during their hospitalization (3 deaths were attributable to COVID-19), and 10 (59%) recovered and were discharged. From December 22nd, 2021, through February 1st, 2022, 9 HO-COVID-19 were discovered during the Omicron variant surge. Six (67%) of these patients were symptomatic, 8 (89%) had a link to an infected employee, 2 (22%) died (1 death was attributed to COVID-19), and 7 (78%) recovered and were discharged.

The Omicron variant surge led to marked increases in HO-COVID-19 despite the continuous adoption of enhanced infection control practices, testing on admission, and daily symptoms screening of patients and employees.

P30

The impact of the COVID-19 pandemic on hospital-acquired infections at a comprehensive cancer center

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Robust infection control (IC) measures were deployed across healthcare institutions at the start of the COVID-19 pandemic, resulting in increased use of personal protective equipment (PPE), enhanced contact precautions, and emphasis on hand hygiene. The impact of these IC measures on the rates of hospital-acquired infections (HAIs), such as multidrug-resistant organisms (MDROs), device-related infections (DRIs), *Clostridium difficile* infection (CDI), and respiratory viral infections (RVIs) is not known. Here, we evaluated the effect of the enhanced IC practices on the occurrence of HAIs in a comprehensive cancer center.

We analyzed the monthly HAIs rates from September 2017 through March 2022, including data 42 months pre-pandemic and 24 months during the pandemic. The incidence rate ratios (IRR) were calculated for all HAIs.

When comparing pre-pandemic to the pandemic period, a significant increase in the overall incidence rate (IR) of MDROs from 0.56 to 0.67 per 1,000 patient days with an IRR of 1.19 (95% CI 1.02-1.39), a decrease in the IR of CLABSIs and a stable IR of CAUTIs and VAEs were observed. A significant decrease was observed in the IR of CDI (IRR 0.65 (95% CI 0.55-0.78)). The total IR of hospital-acquired RVIs per 1,000 admissions (5.24 to 1.82; IRR 0.36; 95% CI 0.30-0.44) decreased.

Implementing strict IC measures during the COVID-19 pandemic in a cancer hospital led to a significant decrease in many HAIs and a reduction in nosocomial RVIs. However, whether these enhanced

measures are needed during the upcoming respiratory viral seasons is not known.

P31

Non-cytolytic viral vaccine vectors induce type I interferon and establish long-lived effector-differentiated CD8 T cell memory

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Background: Effector memory CD8 T cells (T_{EM}) can limit early pathogen spread, but the induction of sustained T_{EM} responses represents a challenging task in vaccinology. Replication-deficient lymphocytic choriomengitis virus (rLCMV) vectors are non-cytolytic and induce long-lived T_{EM}-biased responses, whereas vesicular stomatitis virus (rVSV) based vaccine vectors are cytolytic and elicit CD8 T cell responses of shorter duration with a lower proportion of T_{EM} cells.

Aims and Methods: To investigate whether non-cytolytic behaviour, duration of antigen expression or type I interferon (IFN-) induction determined T_{EM} responses, we mutated the rVSV matrix protein (rVSVMq) to render it non-cytolytic. IFN-I antagonist proteins were incorporated to augment viral antigen expression.

Results: CD8 T cell responses to non-cytolytic rVSVMq vectors in mice resembled those to rLCMV. They contracted less than those to rVSV and they comprised a higher T_{EM} proportion. Unlike rLCMV, which expressed detectable levels of transgenic cargo for ~2 weeks, both VSVdG and VSVMqdG were eliminated within a 5-day window. However, non-cytolytic rLCMV and rVSVMq but not cytolytic rVSV induced substantial systemic IFN-I. IFN antagonist-expressing rVSVMq induced more prolonged serum IFN-I albeit without a detectable impact on T cell response magnitude and T_{EM} differentiation.

Conclusions: Non-cytolytic viral vector behaviour is linked to the ability of eliciting substantial systemic IFN-I and determines the capacity to induce sustained T_{EM}-biased CD8 T cell responses largely independently of vector persistence.

P32

Mucormycosis in children with hematological malignancies is a salvageable disease

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Mucormycosis is emerging as an significant cause of severe morbidity and mortality in immunocompromised patients. contemporary data in children are lacking

We conducted a nationwide multicenter study to investigate the caracteristics of mucormycosis in children with hematological malignancies

The cohort included 39 children with mucormycosis 25 of 1136 children with acute leukemias prospectively enrolled in a centralized clinical registry in 2004-2017 and an 14 children with leukemia identified by retrospective search of the databases of 7 pediatric hematology centers

92% of mucormycosis cases ocurred in patients with acute leukemias.We note a association of mucormycosis with high risk acute lymphoblastic leukemia(ALL) (OR 3.61;95% CI 1.46-8/97;p = 0.005) and with increasing age (OR 3.68;95%CI 1.28-10;P = 0.01)In patients with ALL mucormycosis occurred mainly(65%) during induction. The most common pattern of infection was sino-orbito-cerebral(SOC) (59%). 15 patients (38%) died of mucormycosis,14 within 12 weeks of diagnosis SOC pattern was independently associated with improved 12 week survival(OR 11.26;95%ci1.96-64.82;P = 0.006) and refractory underlying malignancy was associated with increased 12 week mortality(OR 8.9;95%CI1/23-65.05;p = 0.03)In patients receiving frontline therapy for they malignancy(24%) one year mucormycosis related mortality was 21_+8% and 5 year overral survival was 70+_8%

This largest pediatric population based study of mucormycosis demostrates that patients receiving frontline therapy for their malignancy and patients with a SOC pattern are often salvageable.

P33

Human monoclonal antibodies to the spike subdomain 1 neutralize SARS-CoV-2 and its variants of concern

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Progress in the fight against COVID-19 is jeopardized by the emergence of SARS-CoV-2 variants that diminish or abolish the efficacy of vaccines and antiviral monoclonal antibodies. Novel immune therapies are therefore needed, that are broadly effective against present and future coronavirus threats. In principle, this could be achieved by focusing on portions of the virus that are both functionally relevant and averse to change. The Subdomain 1 (SD1) of SARS-CoV-2 Spike protein is adjacent to the RBD and its sequence is conserved across SARS-CoV-2 variants, except for substitutions A570D in Alpha (B.1.1.7) and T547K in Omicron BA.1 (B.1.1.529). In order to specifically identify and study human antibodies targeting SD1, we designed a flow cytometry-based strategy that combines negative selection of B cells binding to the Receptor Binding Domain (RBD) with positive selection of those binding to SD1-RBD fusion protein. Among the 15 produced human monoclonal antibodies, 6 are SD1-specific. 3 of them cross-react with SD1-RBDs corresponding to all six variants of concern and 2 are neutralizing SARS-CoV-2 pseudovirus. Antibody sd1.040 also neutralizes Delta, Omicron BA.1 and Omicron BA.2 pseudovirus, synergizes with an antibody to the RBD for neutralization, and protects mice when present in a bispecific antibody. Thus, naturally occurring antibodies can neutralize SARS-CoV-2 variants by binding to SD1 and can act synergistically against SARS-CoV-2 in preclinical models.

P34

Retrospective analysis of 117 cases of invasive mucormycosis in a tertiary care hospital

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Background: Diagnosis and treatment of mucormycosis remain difficult.

Aim: To review cases of mucormycosis over 29 years in our center.

Methods: Cases were classified in invasive mucormycosis according to EORTC/MSGERC 2020 criteria. Positive serum, BAL fluid or tissue PCR was accepted as a mycological criterion.

Results: 117 mucormycosis were identified. Underlying conditions were mostly hematological malignancy (60), allogeneic hematopoietic stem cell (19) or solid organ (13) transplant. Main other risk factors were chemotherapy (68), T-cell immunosuppressant (58), neutropenia (56), steroids (52), and diabetes (30). Primary site of infection was upper or lower respiratory tract (98), digestive tract (11) and soft tissue (8). *Lichtheimia* was the most frequent genus. PCR (serum, BAL, tissue) was performed in 49 patients and was positive in 41. Fifty-four patients had a concomitant other mold infection, mostly aspergillosis. First-line Mucorales active therapy was amphotericin B (AmB) deoxycholate (7), AmB lipid complex (6), liposomal

AmB (76), posaconazole or isavuconazole (8). Twenty patients received no Mucorales active therapy. Half of them received voriconazole mostly because of a concomitant aspergillosis diagnosed before mucormycosis. Thirty-nine patients underwent surgery. Twelve-week mortality was 61.5% with a decrease over time (1993-2006: 80.0%; 2007-2021: 56.5%).

Conclusions: Mortality decreased over time but remains high. Concomitant other mold diseases are very frequent, complexifying mucormycosis diagnosis. This may result in inappropriate therapy.

P35

Human neutralizing antibodies to SARS-CoV-2 mutational coldspots that broadly crossreact with Orthocoronavirinae

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Most SARS-CoV-2 neutralizing antibodies described to date target the receptor binding and N-terminal domains (RBD and NTD) of the Spike (S) protein. However, mutations such as those found in SARS-CoV-2 variants of concern (VOC), cause amino acid (aa) changes in the RBD and NTD that diminish or abrogate the effectiveness of vaccines and antiviral monoclonal antibodies that are currently in the clinic. We hypothesized that regions of S may be under selective pressure to maintain their aa sequence unchanged because they are essential for its function. We identified 15 regions with infrequent aa changes and devoid of aa changes in SARS-CoV-2 VOC: one coldspot includes the S2' cleavage site and a portion of the fusion peptide (FP), a second one is at the stem helix that precedes the heptad repeat 2 region (HR2). We specifically searched for and identified human antibodies targeting FP and HR2 coldspots in plasma samples from a COVID-19 convalescent cohort. Neutralizing antibodies to the FP are broadly cross-reactive against all human coronaviruses and non-human coronaviruses of the four genera (alpha to delta). Antibody hr2.016, which binds to a conserved epitope near the HR2 helix, neutralizes SARS-CoV-2 variants of concern and is superior to previously described antibodies to this region. Thus, coldspot-guided antibody discovery reveals natural neutralizing antibodies that are broadly cross-reactive with Orthocoronavirinae, including SARS-CoV-2 variants.

P36

Nanoparticles: efficient, safe and affordable platforms for developing vaccines against coronaviruses

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Introduction: Vaccines need to be rationally designed to be delivered to the immune system for maximizing induction of dynamic immune responses. Virus-like nanoparticles (VLPs) are ideal platforms for such 3D vaccines. Coronaviruses have recently gained a lot of attention, due to the ongoing pandemic caused by SARS-CoV-2 and previous endemics by MERS-CoV.

Methods: We have provided proof of concepts in murine models for effective development of VLP-based vaccines against MERS-CoV and SASR-CoV-2. We have used chemical conjugation or genetic fusion techniques to display receptor-binding domain or motif on our immunologically optimized ($CuMV_{TT}$-VLPs). These VLPs incorporate a tetanus toxin epitope and ssRNA, TLR7/8 ligands. The vaccines were tested in murine models.

Results: The vaccines are stable for more than a year at 4°C and highly scalable. Vaccination using subcutaneous or intranasal routes are feasible with nanoparticles. We demonstrated that these vaccines are highly immunogenic in mice as well as rabbits and can induce high avidity antibodies compared to convalescent human sera. Furthermore, the induced antibodies are cross-reactive with different VoCs (in case of SARS-CoV-2). The longevity of the induced immune response lasted longer than 120 days.

Conclusion: Collectively, we show that VLP-based vaccines can efficiently induce high specific anti-RBD and spike antibodies that effectively neutralize different Coronaviruses and their VoCs. As Coronaviruses represent a continuous global threat to human health, it seems rational to further develop these vaccines.

P37

Characterization of the humoral response to Orf virus-vectored immunization

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Recombinant Orf virus (rORFV) based vectors are under clinical development for COVID-19 vaccination. Little is known, however, about the cellular correlates of antibody responses to this poxviral vector platform.

To monitor antigen-specific B cell responses to vaccination, we adoptively transferred to mice indicator populations of monoclonal B cells recognizing the glycoproteins (GPs) of either vesicular stomatitis virus or lymphocytic choriomeningitis virus and epitope variants thereof. Immunizations of mice with rORFV expressing the respective GPs stimulated the transferred B cells to engage in a protracted germinal center (GC) response, which was maintained longer-term when the delivered antigen was of lower affinity. GP-specific CD8 and CD4 T cells responses were also induced, and the latter included T follicular helper cells (Tfh). These T cell responses contracted over time but re-expanded upon homologous rORFV booster vaccination, alongside with an augmentation in antigen-specific memory B cells. Pre-existing rORFV-specific anti-vector immunity suppressed CD8 T cell responses to ORFV-vectored cargo whereas CD4 T cell and B cell responses were unaffected. Importantly, rORFV-based vaccination conferred long-term antibody-mediated protection against VSV challenge.

This study demonstrates the versatility of rORFV-vectored vaccination including its capacity to induce substantial GC B cell as well as Tfh responses. Limited interference by anti-vector immunity should facilitate the challenging task of maintaining protective antibody immunity by prime – boost vaccination.

P38

Rezafungin efficacy and safety in immunocompromised patients: subanalyses of the phase 3 trial in treatment of candidemia and invasive candidiasis

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Background: Rezafungin (RZF) once weekly (QWk) is a next-generation echinocandin in development for treatment of candidemia and invasive candidiasis (IC) and for prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp. in BMT.

Aim: The Phase 3 ReSTORE treatment trial (NCT03667690) demonstrated RZF QWk noninferiority to caspofungin (CAS) QD. This subanalysis evaluated efficacy and safety outcomes in patients identified as immunocompromised (immuno-c) during the trial.

Methods: As previously described, adults with confirmed candidemia and/or IC were randomized to RZF QWk (400mg Wk1 then 200mg QWk) or CAS QD for ≥14 days (≤4 wks) with optional oral fluconazole stepdown for CAS. In this subanalysis, immuno-c patients were those with prior and/or concomitant use of immunosuppressants (eg, calcineurin inhibitors, corticosteroids) and/or medical history ongoing at Screening of neutropenia, BMT, SOT, lymphoma, or leukemia.

Results: Of 187 patients (mITT population), 90 were immuno-c as defined.

Results are for those with data available for analyses:

– Day 14 Global Cure
  – Immuno-c: RZF, 51.1% (23/45); CAS, 55.6% (25/45)
  – No immuno-c: RZF, 66.7% (32/48); CAS 65.3% (32/49)
– Day 5 mycological eradication
  – Immuno-c: RZF, 64.4% (29/45); CAS, 51.1% (23/45)
  – No immuno-c: RZF, 72.9% (35/48); CAS, 71.4% (35/49)

Among immuno-c, more had ≥1 AE (96.9%) and ≥1 SAE (64.6%) vs no immuno-c (79.0% and 45.0% respectively).

Conclusions: In this subanalysis of ReSTORE, immune-c status reduced efficacy rates overall but did not change efficacy rate differences between RZF and CAS.

P39

GRP75 deletion in T cells modifies effector function and calcium dynamics

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The activation and differentiation of T cells into effector cells is accompanied by dynamic changes in cellular metabolism. We recently found that **m**itochondria-**e**ndoplasmic **r**eticulum membrane **c**ontact **s**ites (MERCS) function as immune-metabolic hubs in EM CD8$^+$ T cells, orchestrating key signalling events required to recruit HK-I to VDAC – a channel-protein localized on the OMM. This ultrastructure-positioned process promoted metabolite-flux into mitochondria, respiration and interlinked epigenetic remodelling, essential for memory CD8$^+$ T cells rapid response. Tethering of apposed mitochondria and ER membranes is partially mediated by the IP3R-GRP75-VDAC complex. GRP75 deletion revealed a reduction of MERCS abundance in various cell types. The role of MERCS in effector T cell differentiation and function has not fully been resolved. To explore the role of such organellar contact sites in T cell function, we destabilized MERCS in *in vitro* expanded effector T cells by depleting GRP75 expression via CRISPR/CAS9 gene editing. GRP75 deletion diminished MERCS abundance in effector T cells. IFN-g and GrzB production was reduced in GRP75KO cells. CD27 expression was also decreased in KO cells. Using thapsigargin to modulate cytosolic calcium levels, we observed increased and more rapid cytosolic Ca^{2+} buildup in GRP75KO effector T cells. Lastly, spare respiratory capacity was reduced in GRP75 depleted cells, whilst basal respiration was unvaried. These findings suggest an important role of MERCS in effector cells function by regulating calcium dynamics and mitochondrial metabolism.

P40

Tfh response to congenital virus infection enables antibody-mediated viral load control

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Congenitally acquired hepatitis B virus infection in humans and lymphocytic choriomeningitis virus (LCMV) in mice are thought to induce immunological tolerance as a basis for life-long persistence.

We revisited this long-standing dogma and found that neonatally LCMV-infected carrier mice mounted antiviral antibody responses that partially controlled viral loads independently of the tolerized CD8 T cell compartment. When adoptively transferred into carrier, LCMV-specific B cells mounted a vigorous germinal center (GC) response, which depended on follicular CD4 T helper (Tfh) cells, interleukin-21 (IL-21) and the expression of MHC class II as well as CD40 on the transferred B cells, suggesting the availability of cognate T help. Antiviral CD4 T cells were detectable in carrier upon MHC class II tetramer enrichment, with a majority exhibiting a Tfh phenotype. Single cell RNA sequencing revealed that ~20% thereof were classical GC-Tfh cells, expressing elevated levels of CXCR5, PD-1, ICOS and IL-21 but low CCR7 mRNA. These cells, therefore, resembled an analogous subset in adult LCMV-infected animals, but exhibited also distinct transcriptional alterations. Supplementation of specific CD4 T help potentiated B cell responses in congenitally infected carriers but not in adult infected animals.

Hence, CD4 Tfh cell responses arise in congenitally infected animals and are rate-limiting for virus control. Their numerical insufficiency and transcriptional alterations suggest strategies to augment CD4 T cell responses could represent a promising step towards a functional cure.

P41

Clinical usefulness of teicoplanin therapeutic drug monitoring in cancer patients

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Background: Teicoplanin is a glycopeptide antimicrobial with structural similarity to vancomycin. It has been reported variability in drug concentrations after standard dosage regimens. However, there is limited information about the usefulness of teicoplanin therapeutic drug monitoring (TDM) in cancer patients.

Aims: This study aimed to investigate the usefulness of teicoplanin TDM in cancer patients.

Methods: In this prospective observational study, we conducted TDM of teicoplanin in cancer patients undergoing active anticancer treatment in Korea. The primary endpoint was all-cause mortality at 4 weeks, and the secondary endpoints were clinical response at the end of teicoplanin therapy and safety.

Results: A total of 58 trough concentrations were measured in 22 patients from March 2017 to February 2022. All-cause mortality at 4 weeks was 18.2%, and clinical response at the end of teicoplanin was successful in 73% of patients. There was no significant relationship between trough concentrations of teicoplanin and all-cause mortality at 4 weeks (median [range], 5.9 mg/L [5.3-16.3] in non-survivors *vs*. 9.3 mg/L [3.2-41.5] in survivors; $P = 0.459$). Trough concentration of teicoplanin did not differ according to the clinical response at the end of therapy. There were no significant adverse events.

Conclusions: This study does not show any relationship between trough concentrations of teicoplanin and clinical outcomes in cancer patients. However, to prove the usefulness of teicoplanin TDM, well-designed, large-scale clinical studies are required.

P42

Outcome of severe acute respiratory syndrome coronavirus 2 infection and risk factors for the development of pneumonia in patients with lymphoma

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Background: Although patients with lymphoma appear to be particularly vulnerable to SARS-CoV-2, clinical evolution of COVID-19 in lymphoma has been under-represented.

Purpose: To investigate the outcome of SARS-CoV-2 in patients with lymphoma and the risk factors for COVID-19 pneumonia.

Methods: Among adult patients with lymphoma at Yeouido St. Mary's hospital, we retrospectively reviewed the medical records with diagnosis of SARS-CoV-2 from January 2020 to April 2022.

Results: A total of 117 patients (64 males) with median age of 53 years were identified. Sixty-eight were in complete remission when diagnosed of SARS-CoV-2. Sixty-one had more than one comorbidity and 29 had hypogammaglobulinemia. Thirty-four never had been vaccinated for SARS-CoV-2. During median follow-up of 61 days, COVID-19 pneumonia developed in 37 (31.6%) and 31 had persistent pulmonary conditions even after one month. Overall mortality was 6.0% (7 of 117), of which 4 were infection related. Multivariable

analysis demonstrated that rituximab maintenance theraphy in follicular lymphoma (adj. OR of 3.67, 95% CI, 1.3-10.39, p = 0.01) was significant risk factor for COVID-19 pneumonia. Hypogammaglobulinemia (adj. OR of 2.27, 95% CI, 0.82-6.25, p = 0.08) and never vaccinated (adj. OR of 2.26, 95% CI, 0.85-6.01, p = 0.08) were not.

Conclusions: In patients with lymphoma, SARS-CoV-2 causes pneumonia more frequently and most of them progress to COVID-19 pneumonia. More aggressive vaccination and intervention for patients with lymphoma who have impaired humoral response related to rituximab maintenance, are needed.

P43

Invasive fusariosis in hematologic malignancy patients: 10-year experience in a single hospital

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Introduction: *Fusarium* is a hyaline mold causing opportunistic infection. Invasive fusariosis (IF) is fatal in immunocompromised hosts, but antifungal susceptibility is not well established.

Purpose: In this study, we collected IF cases from the databse in a single institute. We measured the minimum inhibitory concentration (MIC) of the isolates and examined its correlation with patient's clinical outcomes.

Methods: We retrospectively reviewed medical records of patients with culture-proven *Fusarium* infection at Catholic Hematology Hospital from October 2012 through December 2021. Molecular identification of isolates and antifungal susceptibilities were conducted in laboratory.

Results: We identified 19 cases of hematologic patients with IF. The most common underlying disease was acute myeloid leukemia (63.2%). We obtained 21 specimens, 12 of them were blood cultures (63.2%). Thirty day overall mortality was 36.8%, mortality related to IF was 26.3%. Isolates were mainly *Fusarium solani* complex species (68.4%). We tested MIC of antifungal agents in 8 available clinical isolates. MIC of antifungal agents showed difference between species but also within species complex. Patients' survival and recovery from IF were not necessarily related to low MIC.

Conclusion: IF is fatal to immunocompromised host. *Fusarium* exhibits variable MIC to antifungal agents. In vitro MIC does not seem to correlate with survival of patients. Further study is necessary to understand relation between in vitro MIC and clinical outcomes.

P44

Receptor-independent infection by Japanese encephalitis virus-associated human microglia induces cell death of human microvascular endothelial cells

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The neurotropic virus Japanese encephalitis virus (JEV) invades the human central nervous system, inducing neuroinflammation and disruption of the blood-brain barrier. JEV interacts with various cell types including the endothelial cells of the blood-brain barrier. The present works aims to determine the effect of receptor-dependent and independent-infection by JEV on the survival of human microvascular endothelial cells. Receptor-dependent infection of human microvascular endothelial cells by cell-free JEV resulted in virus propagation but was not cytotoxic to the cells. Receptor-independent infection of human microvascular endothelial cells by JEV-associated human microglia in co-culture system resulted in both viral rescue and cytotoxicity to the cells. However, viral transmission from JEV-infected human microglia to human microvascular endothelial cells was independent to the CX_3CR1-CX_3CL1 axis using CX_3CR1 antagonist. Overall, our findings demonstrate that human microvascular endothelial cells participate in virus propagation but only JEV-infected microglia may contribute to the disruption of the blood-brain barrier via intercellular viral transmission to endothelial cells.

P45

Effector functions of human TH9 cells depend on PPARg-regulated glucose metabolism

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Background: T_H9 cells are crucial mediators of allergic skin inflammation. They are characterized by expression of IL-9/IL-9R and rely on the transcription factor PPAR-g for full effector function. The functional role of PPAR-g in T_H9 cells, however, remains unknown.

Aim: To use human T_H9 cells as a model population to investigate the mechanism by which PPAR-γ regulates the effector function of human T_H9 cells.

Methods: T_H9 cells were isolated from peripheral blood. Transcriptomic analysis of T cell clones treated with a chemical inhibitor (GW9962) of PPAR-g was performed and further analysis was done by flow cytometry.

Results: We found that PPAR-g is a positive regulator of glycolysis in human T_H9 cells. Accordingly, T_H9 cells featured a higher glycolytic activity as compared to T_H1 and T_H2 cells. In turn, impairment of glycolysis led to downregulation of IL-9, but not IL-13 expression, thus emulating the effects of PPAR-g antagonism on cytokine production. Conversely, enhancing glycolytic activity by increasing glucose availability increased IL-9 levels, while leaving IL-13 expression unchanged. Mechanistically, PPAR-g- and glycolysis-dependent regulation of IL-9 expression was mediated through mTORC1.

Conclusions: Our data propose that PPAR-g is a positive regulator of glucose metabolism in T_H9 cells and that IL-9 expression is specifically dependent on tissue availability of glucose and cellular metabolic activity. These findings highlight a novel link between the metabolic environment in the tissue during inflammation and type 2-driven skin inflammation.

P46

A multi-target nanovaccine confers anti-tumor efficacy against head & neck carcinoma

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Background: Head and Neck cancer (HNC) is the 7th most common cancer worldwide. In the recent decades, the rate of human papilloma virus (HPV)-associated HNC cases have been increasing. Although three prophylactic vaccines against HPV have been approved by the FDA, no therapeutic vaccine is yet available.

Methods: In the current study, we evaluated the immunogenicity of a novel therapeutic multi-target nanoparticle vaccine displaying elongated HPV E6 & E7 T-cell epitopes (~32 a.a.) in a murine HNC model. Peptides were synthesized and covalently coupled to virus-like particles (VLPs). The candidate vaccine Qβ(1668)-HPV_{ag} was further enhanced by packaging non-methylated CpGs, a TLR-9 ligand.

Results: Qβ(1668)-HPV_{ag} abrogated HNC tumor growth, elicited a strong systemic anti-tumor response and enhanced infiltration of T-cells in tumor. It has been recently suggested that dendritic cells (DCs) can polarize $CD8^+$ T-cells into tissue-resident memory T-cells. Accordingly, we have characterized different DCs subsets in tumor microenvironment as well as in periphery upon vaccination. Our results indicate that vaccination with Qβ(1668)-HPV_{ag} increased the percentage of cDC2 in periphery. There was also a trend in increased density of cDC3 subset in tumor microenvironment.

Conclusion: Our multi-target nanovaccine shows a promising anti-tumor effect in an aggressive HNC murine model. Future clinical application using this strategy is readily feasible, as click chemistry coupling of synthetic peptides to nanoparticles can be done at the bedside directly before injection.

P47

Intranasal administration of a VLP-based vaccine induces neutralizing antibodies against SARS-CoV-2 and variants of concern

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Background: The highly contagious SARS-CoV-2 is mainly transmitted by respiratory droplets and aerosols. Consequently, people are required to wear masks and maintain a social distance to avoid spreading of the virus. Despite the success of the commercially available vaccines, the virus is still uncontained globally. Given the tropism of SARS-CoV-2, a mucosal immune reaction would help to reduce viral shedding and transmission locally. Only seven out of hundreds of ongoing clinical trials are testing the intranasal delivery of a vaccine against COVID-19.

Methods: In the current study, we evaluated the immunogenicity of a traditional vaccine platform based on virus-like particles (VLPs) displaying RBD of SARS-CoV-2 for intranasal administration in a murine model. The candidate vaccine platform, $CuMV_{TT}$-RBD, has been optimized to incorporate a universal T helper cell epitope derived from tetanus-toxin and is self-adjuvanted with TLR7/8 ligands.

Results: $CuMV_{TT}$-RBD vaccine elicited a strong systemic RBD- and spike- IgG and IgA antibodies of high avidity. Local immune response was assessed and our results demonstrate a strong mucosal antibody and plasma cell production in lung tissue. Furthermore, the induced systemic antibodies could efficiently recognize and neutralize different variants of concern (VOCs) of mutated SARS-CoV-2 RBDs.

Conclusion: Our data demonstrate that intranasal administration of $CuMV_{TT}$-RBD induces a protective systemic and local specific antibody response against SARS-CoV-2 and its VOCs.

P48

A novel virus-like particle platform for the treatment of peanut allergy: mechanistic insights

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Background: Peanut allergy is a frequent disease affecting all age groups but develops typically early in life. In most cases peanut allergy does not resolve with age and could become a serious health-threat as small amounts of peanut can induce strong allergic reactions (anaphylaxis). Studies indicated that in particular, Ara h 2 is recognised by IgE from more than 95% of peanut-sensitive patients.

Methods: We constructed a new vaccine, VLP Peanut, based on the cucumber mosaic virus-like particles ($CuMV_{TT}$), genetically fused with Ara h 2 ($CuMV_{TT}$-Arah2) and encapsulated prokaryotic RNA serving as a TLR 7/8 ligand.

Results: VLP Peanut vaccination induced a robust Ara h 2 specific IgG response in mice. Thereby, the formation of high avidity IgG antibodies and IgG2c subclass antibodies was heavily dependent on TLR7 signalling triggered by the vaccine's incorporated RNA. Systemic protection by VLP Peanut was confirmed in mice challenged with whole peanut extract after vaccination or passive immunization. Interestingly, the provided protection was dependent on IgG antibodies and the FcgRIIb receptor.

Conclusions: The VLP Peanut vaccine provides strong evidence for the generation of high levels of IgG antibodies specific for a single allergen (e.g. Ara h 2) and that protection may be conferred against complex allergen mixtures. This vaccine candidate is scheduled to enter clinical studies for therapeutic vaccination of humans with peanut allergy in 2022.

P49

Anti-IAPP monoclonal antibody improves clinical symptoms in a mouse model of type 2 diabetes

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Background: Type 2 Diabetes Mellitus (T2DM) is a chronic progressive disease, defined by insulin resistance and insufficient insulin secretion to maintain normoglycemia. Amyloidogenic aggregates are a hallmark of T2DM patients; they are cytotoxic for the insulin producing β-cells, and cause inflammasome-dependent secretion of IL-1β.

Aim: To avoid the associated β-cell loss and inflammation in advanced stage T2DM, we developed a novel monoclonal therapy targeting the major component of aggregates, islet amyloid polypeptide (IAPP).

Results: The here described monoclonal antibody (mAb) m81, specific for oligomeric and fibrils, but not for soluble free IAPP, is able to prevent oligomer growth and aggregate formation in vitro, and blocks islet inflammation and disease progression in vivo.

Conclusion: Collectively, our data show that blocking fibril formation and prevention of new amyloidogenic aggregates by monoclonal antibody therapy may be a potential therapy for T2DM.

P50

SP110 expression analysis facilitates the detection of human patients with type I interferon signatures

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Background: The Speckled Protein 110 (SP110) encodes a PML nuclear body protein with yet to be determined cellular functions. Genetically determined loss of Sp110 expression causes a highly lethal combined immunodeficiency and liver failure (veno-occlusive disease with immunodeficiency, VODI).

Aims: As SP110 is an interferon stimulated gene, we were interested to find out whether SP110 may represent a suitable marker to reflect the in vivo interferon signature in patients with immune dysregulation.

Methods: SP110 mRNA expression was analyzed in peripheral blood of 60 healthy controls or 60 patients with immune-dysregulation by real-time PCR together with known interferon-stimulated genes (MX1, IFIT1, ISG15, SIGLEC1, RSAD2, IFI44). Patients with defined interferonopathy due to SAMHD1 mutation served as positive controls. SP110 protein expression with and without interferon alpha stimulation was measured in SP110 competent vs. deficient Jurkat T cells and PBMC derived T cells.

Results: Sp110 expression increased on mRNA and protein level following interferon alpha stimulation identifying it as an interferon stimulated genes (ISG). SP110 mRNA expression was significantly elevated in patients with immune dysregulation compared to healthy controls. When compared to established ISG's SP110 outcompeted MX1, IFIT1 and IFI44 in its ability to identify type I interferon signatures in patients with immune-dysregulation.

Conclusions: Our work establishes Sp110 as an easy to measure biomarker of type I interferon signatures *in vivo* and suggest to implement it in future interferon signature panel analysis.

P51

T cell phenotype of patients with drug reaction with eosinophilia and systemic symptoms shows signs of chronic activation even after resolution

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Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe multi-organ drug hypersensitivity reaction (DHR) involving T cells. DRESS patients are at risk of subsequent drug exposure leading to further DHR, resulting in a multiple drug hypersensitivity syndrome (MDH).

Objectives: This project aims to characterize DRESS patients with and without MDH to recognize which patients are at risk of further DHR.

Methods: In this prospective multicentre explorative study, we investigated the clinical picture, the T cell activation phenotype after DHR resolution and *in vitro* cytokine release of patients' leukocytes to tested drugs (cyto-LTT). Four groups were investigated: 8 DRESS without MDH (mono-DRESS), 13 DRESS with MDH (DRESS/MDH), 5 maculopapular exanthema and 5 healthy controls (HC).

Results: DRESS culprit drugs belonged to β-lactam antibiotics (12/21), non-β-lactam antibiotics (7/21) and antiepileptic drugs (3/21). All subjects were sensitized in cyto-LTT, while 14/21 were sensitized in patch test. DRESS patients' T cells show signs of chronic activation even during homeostasis compared to HC, with increased CD69 and PD-1 but reduced CD38 and OX-40. Based on T cell activation markers, DRESS/MDH is indistinct from mono-DRESS. Cyto-LTT with culprit drugs revealed a dominance of IL-5 release, with 10X more cytokines produced by MDH/DRESS patients' leukocytes.

Conclusion: DRESS patients' T cells remain chronically activated after DHR resolution. DRESS with or without MDH are likely the same phenotype, with increased drug exposure increasing the risk for MDH.

P52

Severe combined immunodeficiencies: expanding the mutation spectrum in Turkey and identification of 4 novel variants

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Background and Aims: Human Inborn Errors of Immunity (IEIs) are clinically and genetically heterogeneous groups of diseases, with relatively mild clinical course or severe types that can be life-threatening. Severe combined immunodeficiency(SCID) is the most severe form of IEIs, which is caused by monogenic defects that impair the proliferation and function of T, B, and NK cells. According to the most recent report by the International Union of ImmunologicalSocieties (IUIS), mutations in IL2RG, JAK3, FOXN1, CORO1A, PTPRC, CD3D, CD3E, CD247, ADA, AK2, NHEJ1, LIG4, PRKDC, DCLRE1C, RAG1, and RAG2 genes may cause SCID.

Methods: The targeted next-generation sequencing (TNGS) workflow based on Ion AmpliSeq™ Primary ImmuneDeficiency Research Panel was designed for sequencing 264 IEI-related genes on Ion S5™ Sequencer.

Results: Eight disease-causing variants (4 novel) were identified in 9 patients in 4 different SCID genes, namely IL2RG(n = 4), RAG2 (n = 3), NHEJ1 (n = 1), and DCLRE1C (n = 1) genes between 2019-2021.

Conclusions: Next-generation sequencing allowed a rapid and accurate diagnosis in SCID patients.

P53

IL-9 promotes a pathogenic phenotype and enhances proliferation in a subset of skin-tropic Th2 cells

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Background: IL-9 is a pleiotropic cytokine, for which an overarching role in humans remains elusive. Both interleukin 9 (IL-9) and its receptor, IL-9R, are expressed by skin-tropic T helper 2 (T_H2) cells. This suggests that autocrine or paracrine IL-9 signals play an important role in cutaneous immunity and allergy. Yet, the mechanism of action of IL-9 remains incompletely understood.

Aim: We aimed at deciphering the effect of IL-9 signals on T_H cells in allergic skin inflammation.

Method: We isolated human IL-9R$^+$ T_H cells from acute allergic contact dermatitis and performed transcriptional profiling after stimulation with IL-9.

Results: IL-9 induced differential expression in T_H2 cells of approx. 800 genes. Upregulated genes were associated with conventional T_H2 immune response and, strikingly, included genes specifically associated with the pathogenic T_H2 phenotype, such as *IL9*, *IL17RB* and *HPGDS*. In addition, IL-9-stimulated T_H2 cells showed a coordinated induction of genes involved in aerobic glycolysis. At the protein level, we confirmed that IL-9 prominently induced the expression of the monocarboxylate transporter 1 (MCT1), which is key for the export of lactate. Functionally, IL-9 boosted glycolytic capacity and proliferation, which was abolished by MCT1 inhibition.

Conclusion: Our data uncovers that IL-9 not only promotes pathogenic features, but also provides a proliferative advantage in a subset of skin-tropic T_H2 cells. This hitherto unrecognized role of IL-9 might open up novel strategies for targeted manipulation of T_H cells in allergic skin inflammation.

P54

Rezafungin in vitro activity against Candida spp. causing invasive infections in hematology/oncology and transplant units worldwide (2014-2021)

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Background: Patients undergoing onco-hematologic, and/or transplant therapy are at risk for invasive candidiasis (IC) and require appropriate antifungal treatment that are efficacious, safe, and compatible with other medications.

Purpose: The *in vitro* activity of rezafungin (RZF), a new echinocandin, was evaluated against *Candida* spp. isolates causing IC in patients from onco-hematology and transplant units (HTU).

Methods: 462 *Candida* spp. (1/patient) were collected from HTU patients in 48 hospitals worldwide during 2014-2021. Isolates were identified by MALDI-TOF and/or sequencing methods, then susceptibility tested by CLSI reference broth microdilution. CLSI breakpoints (BP), including provisional susceptible (S) rezafungin BP, were applied.

Results: *C. albicans* (CA, 39.4%) was the most common organism, followed by *C. glabrata* (CG, 19.3%), *C. parapsilosis* (CP, 14.3%), *C. tropicalis* (CT, 13.2%), *C. krusei* (CK, 10.8%), and *C. dubliniensis* (CD, 3.0%). RZF inhibited the growth of 97.8% of CG and 100% of CA, CP, CT, CK, and CD at the susceptible BP. RZF *in vitro* activity was similar to other echinocandins against *Candida* spp. (93.3-100%S) with available BP. Only 2 CG isolates were non-susceptible to RZF (MIC, 2 mg/L). Fluconazole resistance (FLC-R) was observed in 35 *Candida* isolates, including 18 CG (20.2%), 10 CP (15.2%), 4 CT (6.6%), and 3 CA (1.6%). All FLC-R isolates were susceptible to RZF.

Conclusions: RZF showed *in vitro* activity against *Candida* spp. isolates recovered from HTUs worldwide. The FLC-R rate was high, but RZF was active against all FLC-R isolates.

P55

A case with combined immunodeficiency due to a homozygous SPPL2a mutation

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Background: The intramembrane protease signal-peptide-peptidase-like 2a(SPPL2a) resides in lysosomes and endosomes and has been implicated in the processing of type 2 transmembrane proteins including TNF-alpha, Fas ligand and the invariant chain of the MHCII complex. It has been shown that SPPL2a-/-mice are characterized by a developmental arrest of B cells at the transitional stage1. Inherited SSPL2a deficiency leading to susceptibility to mycobacterial disease due to decreased number of cDC2s and impaired IFN-gamma production is reported in few patients.

Case Report: A 10-year-old girl, born to first-degree consanguineous parents, was admitted with upper respiratory tract infections and otitis media 7-8 times/year since 6 years of age. She had multiple cervical <1 cm lymphadenopathies with enlarged tonsils and one BCG scar. Laboratory investigations showed hypogammaglobulinemia (IgG <137mg/dl, IgA <6mg/dl). IgM was normal. Lymphocyte immunophenotyping revealed inverted CD4/CD8 ratio, decreased CD3+CD4+CD45RA+CD31+T cells and class-switched B cells. In vitro T cell proliferative response to PHA was low. Quantiferon-TB test was negative. A homozygous c.262G >A(p.Val881Ile) mutation in the SSPL2A gene was detected by targeted next-generation sequencing of a primary immunodeficiency panel. She is doing well under regular IgG replacement.

Conclusion: The patient with a homozygous SPPL2a mutation is presented to emphasize that the phenotype related to this gene may differ in humans. Further functional studies are warranted to shed more light on the pathogenesis of SPPL2a deficiency.

P56

Clostridioides difficile infections among allogeneic hematopoietic cell transplant recipients in Switzerland, 2009-2019

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Background: Patients undergoing allogeneic stem cell transplant (allo-HCT) are at high risk for *Clostridioides difficile* infection (CDI). The incidence and recurrence rates may vary according to local epidemiology and management.

Aims: To describe CDI epidemiology among allo-HCT recipients in Switzerland and to analyze risk factors for recurrence.

Methods: Multicenter study including 1540 allo-HCT recipients from the Swiss Transplant Cohort Study between 2009-19. Pertinent clinical data of CDI episodes were collected. Logistic regression analysis was performed to identify risk factors for recurrence.

Results: 150 episodes of CDI occurred in 131 patients with an overall incidence of 9%. Median age was 51 years (41-62) and 60% were male. The most frequent underlying disease was acute myeloid leukemia (44%). Twenty-two cases (15%) were classified as severe according to the Zar-Score. Metronidazole was used in 65% of the cases, oral vancomycin in 17%. Overall, 30-day mortality was 7%. CDI recurrence occurred in 27 patients (18%). Underlying disease other than acute leukemia, intestinal graft-versus-host disease and prior intravenous vancomycin were independently associated with recurrence.

Conclusions: CDI incidence and risk factors for recurrence among allo-HCT recipients in Switzerland are in line with previous reports from other countries. Despite the high use of metronidazole, the incidence of recurrent CDI was not higher compared to other patient populations. Further studies are required to identify patients likely to benefit most from novel treatment options targeting recurrent CDI.

P57

Utilization of commercial multiplex gastrointestinal panels for diagnosing acute diarrhea in hospitalized patients with immunocompromised conditions

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Objectives: To evaluate the clinical utilization of multiplex real-time (rt) PCR gastrointestinal (GI) panel for diagnosing acute diarrhea among hospitalized patients.

Methods: Hospitalized patients admitted during December 2016—2018 who had acute diarrhea ≥3 days were enrolled. Patient's stool specimens were sent for routine microbiological testing and for two commercial multiplex rt-PCR assays—Allplex (AP) and FilmArray (FA) GI panels.

Results: 199 patients were enrolled; 92 (46.5 %) were male, and the mean age was 66.3 years. Common immunocompromised conditions were having immunosuppressive therapy (42.4%), diabetes mellitus (40.4%), kidney disease (29.8%), malignancy (28.1%), and autoimmune disease (9.6%). Only 4.5% of conventional stool cultures were positive, whereas 24.6% and 20.1% of stool samples were positive by the AP and the FA panels, respectively. Common agents detected by the AP were *Aeromonas* spp. (32.9%), *C. difficile* (18.6%), enteropathogenic *E. coli* (EPEC) (14.3%), and *Salmonella* spp. (10.0%), while the FA detected EPEC (26.5%), *C. difficile* (20.3%), and *Salmonella* spp. (12.5%). FA do not include *Aeromonas* target that caused the discordant results between the two testing. Target co-detections (≥2) were 24.5% by the AP and were 35.0% by the FA assays. Fever, watery diarrhea and previous antibiotic use were factors independently associated with the GI panel testing negative.

Conclusions: Multiplex GI panels have clinical utility to detect more enteric pathogens in hospitalized patients compared to the conventional testing.

P58

Levofloxacin versus amoxicillin/clavulanate and ciprofloxacin in the outpatient management of low-risk febrile neutropenia in children; a pilot study

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Background: Outpatient management of low-risk fever and neutropenia should be implemented if close monitoring is accessible and patient compliance is feasible. We aim to assess the efficacy of single-agent Levofloxacin versus the Augmentin /ciprofloxacin regimen used in our institute.

Methods: This is a randomized prospective interventional 2 arm study of low-risk febrile neutropenia patients presenting to the emergency department at the National Cancer Institute, Cairo University starting from December 2021 to January 2023. Follow up of the outpatient cases at; Day 1: Start oral antibiotics, obtain guardians contacts, and assure compliance, Day 3: Follow up the patient clinically and count, and Day 7: Resolution of infection and stopping of antibiotics regardless of neutropenia. Primary outcomes include Safe marrow recovery and improvement of fever in all eligible patients.

Results: preliminary analysis of the first 30 patients (15 in each group) was done. 100% of patients achieved marrow recovery in both arms by D7. Fever subsided in 100% on the Levofloxacin arm compared to 60% in the group receiving Augmentin/Ciprofloxacin. only one patient on the double agent arm was upgraded to HR and admitted to the inpatient. Levofloxacin was tolerable in all patients with no significant side effects.

Conclusions: Levofloxacin has better efficacy and can be administered safely in children with low-risk FN. close follow-up for long-term side effects and monitoring of possible emerging bacterial resistance is warranted.

P59

Stem cell memory EBV-specific adoptively transferred T cells control EBV posttransplant lymphoproliferative disease growth in vivo

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Epstein Barr virus (EBV)-driven post-transplant lymphoproliferative diseases (PTLD) are associated with poor prognosis. Infusion of EBV-specific cytotoxic T-cell lines (CTLs) increases overall survival, but ~30% of patients show no response indicating a need for further improvements. Recent findings show that adoptively transferred early differentiated T cells (stem cell memory T cells, T_{SCM}) improve the prognosis in chronic viral diseases and are associated with effective and durable anti-tumor responses. T_{SCM} might be superior to highly differentiated T cells due to their longevity and robust proliferative potential.

We developed a protocol to expand T_{SCM}-enriched peptide-stimulated EBV-specific T cells (CTL-R) within 10 days. These were compared with EBV-CTLs stimulated with EBV-transformed lymphoblastoid cell lines (LCL) and expanded over 28 days (CTL-L). *In vitro* analysis showed an earlier differentiated and less exhausted phenotype of CTL-R compared to CTL-L. While specificity to latent EBV antigens was similar between both groups, CTL-R expand lytic antigen-specific T cells more frequently than CTL-L.

In *in vivo* experiments, both groups of expanded EBV CTLs showed successful tumor control after 27 days. Compared to CTL-L, CTL-R proliferated and persisted in organs (blood, spleen, bone marrow).

These findings demonstrate that expanded EBV-specific T_{SCM}-CTLs have favorable properties such as non-exhausted, early differentiated T cells targeting lytic and latent EBV antigens, which could be beneficial for a variety of adoptive virus-specific T-cell therapy indications.

P60

Exercise-induced anaphylaxis to saffron

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Background: Allergies to spices account for ~2% of food allergies. One case of saffron anaphylaxis was described by Wüthrich. Saffron is a known cause of occupational respiratory allergy in saffron pickers.

Aim: We present an atopic female with III° anaphylaxis 1.5 hrs after a saffron-containing rice dish while dancing. No other co-factors were present. NSAID were taken after the start of the reaction and the same were tolerated again since.

Methods: Type I sensitization was shown to saffron by prick-to-prick test, and to grasspollen and mugwort by pricktest and sIgE. sIgE-assays for saffron and its components Cro s1 (ole-e1-like protein), Cro s2 (profilin) and Cro s3 (nsLTP) are not commercially available. Potentially cross-reacting IgE to profilins, LTP and an ole-e1 like protein from other sources were not found. A basophil activation test (BAT) with saffron induced degranulation in 30% of the basophils. Sensitizations to other ingested foods were excluded. Oral provocation was deemed too risky.

Results: Sensitization to saffron was shown in prick test and BAT, but no cross-reacting determinant from other sources was found. It was impossible to infer the eliciting allergenic component. Genuine saffron sensitization is thus likely. In view of the sensitization to mugwort pollen, cross-reactivity to an unknown mutual antigen can't be excluded.

Conclusion: To our knowledge this is the 2nd case of anaphylaxis to saffron. Physical exertion is a likely cofactor. The allergenic determinants incriminated in respiratory saffron allergy seem not to be involved in this case of anaphylaxis.

P61

Therapeutic approach using T and NK-92 cells modified with chimeric antigen receptors (CAR) specific to Cryptococcus neoformans.

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Cryptococcus neoformans is an opportunistic fungal pathogen affecting immunocompromised individuals, mainly those infected with HIV, and about one million cases/year of meningoencephalitis are reported resulting in 625,000 deaths in the world. Current therapies to treat cryptococcosis lead to adverse side effects and increased antifungal drugs resistance in *Cryptococcus* spp. Cell therapy using chimeric antigen receptor (CAR)-modified T or NK-92 cells is a promising therapeutic approach to cryptococcosis. GXMR-CARs, *Cryptococcus* spp. GXM-specific, composed of distinct recognition portions (scFv), scFv1-GXMR-CAR and scFv2-GXMR-CAR, were expressed by Jurkat and NK-92 cells after transduction. scFv1-GXMR-CAR or scFv2-GXMR-CAR recognize soluble GXM, and these receptors mediated high levels of IL-2 by Jurkat cells incubated with *C. neoformans*. scFv1-GXMR-CAR and scFv2-GXMR-CAR induced high levels of IL-2 in the absence of ligand that characterize the tonic signaling, which is more pronounced by scFv1-GXMR-CAR. Tonic signaling triggered by scFv1-GXMR-CAR and scFv2-GXMR-CAR and the activation of modified cells with these receptors in response to *C. neoformans* yeast are mitigated by Dasatinib, a protein kinase inhibitor. NK-92 expressing scFv1-GXMR-CAR or scFv2-GXMR-CAR had high levels of IFN-γ in the lack of ligand, and a significant production of IFN-γ was mediated by both GXMR-CARs against *C. neoformans*. scFv2-GXMR-CAR NK-92 cells compromised the amphotericin B resistance of *C. neoformans*. GXMR-CAR containing scFv2 is a great candidate to cell therapy using CAR technology.

P62

IgE glycosylation is essential for the activity of omalizumab

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Omalizumab is the only approved therapeutical antibody against IgE. It is well-studied and widely used for allergic conditions like severe asthma, CSU, and nasal polyps. Omalizumab binds free IgE, which prevents the sensitization of effector cells and promotes the down-regulation of FceRI. Recent studies described the importance of IgE glycosylation for binding to the FceRI. Since the binding sites of omalizumab and FceRI to IgE overlap, we addressed whether IgE glycosylation also affects omalizumab's ability to bind IgE.

To investigate this question, we used IgE from four sources: one recombinant IgE, two monoclonal IgE from hybridomas, and IgE isolated from human serum. We used PNGase F to remove all glycans and Endo F1 to remove the oligomannose structure, which is essential for binding to FceRI. We analyzed binding, affinity, and blocking ability using ELISA, BioLayer Interferometry, and B cell assays. The results show that omalizumab binds IgE in a glycan-dependent manner. Interestingly, removing the oligomannose alone reduces the activity of omalizumab drastically. To confirm our results, we produced a mutant IgE (N394Q) that lacks the oligamannose genetically. Importantly, this mutation completely abrogated omalizumab's activity. Our results suggest that IgE glycosylation is essential for the efficacy of omalizumab. This insight could explain why some patients do not respond to omalizumab. A difference between responders and non-responders could be due to the different glycosylation of IgE. This insight may help in the development of new therapeutic antibodies.

P63

Keep one's eye on lentils: a descriptive case series of pediatric patients with lentil allergy or sensitization

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Background: Diet trends promote legumes as important protein supplements. Thus, non-priority legumes, e.g. lentils, are an increasing cause of allergic reactions.

Aim: Describe clinical features of a Swiss pediatric population allergic to lentils and evaluate the necessity to integrate non-priority legumes in a standard allergy work-up.

Methods: We screened and described retrospectively patients of our pediatric allergy department for allergy/sensitization to lentils from 2018-2022. Food allergy severity score (oFASS) was used to grade reactions.

Results: 22 children with allergy (18/22) or sensitization (4/22) to lentils were studied. 5/18 patients presented mild, 10/18 moderate and 3/18 severe allergic reactions. One moderate and all severe reactions happened at day care. In these families lentils were rarely or not consumed at home. The mean age at the time of reaction was 3.3y and of diagnosis 5.9y. 90% showed allergic reactions or sensitization to other legumes. Patients showed high percentage of atopic disease in their own and family history (100%, 90%). The mean sIgE was 6.97kU/L and the skin prick test was in 69% positive (11/16).

Conclusion: These 22 patients with allergy or sensitization to lentils show a high association with atopic disease and co-allergies to other legumes. Severe allergic reactions to lentils can occur, in our patient population these reactions presented at day care. We suggest to include a screening for non-priority legumes in the standard allergy work-up in the first years of life in patients with other food allergies, even in families without or rare lentil consumption.

P64

Oral immunotherapy for cashew nut and peanut allergy in children 2018-2022 at University Children's Hospital Basel

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Background: Oral immunotherapy (OIT) in children for peanut allergy (PN) is increasingly used, whereas there is limited data on OIT in cashew nut (CN) allergy.

Aim: Side effects of CN compared with PN OIT.

Methods: Retrospective analysis of patients (n = 64) with CN (n = 24) or PN (n = 40) OIT. Side effects during oral food challenge (OFC) (5 steps) were graded using the oFASS-5. The tolerance threshold was defined as the first step of an objective allergic reaction.

Results: Median patient age was 7 years (range 2-17). In the initial threshold-defining OFC, 92% of CN allergic patients had mild to moderate reactions, 8% severe reactions. In PN allergic patients 41% had mild to moderate reactions, 20% severe reactions, 40% had no reactions, with the latter group undergoing a desensitization protocol with lower starting doses. Mean threshold was 0.3g nut protein for CN, and 0.2g for PN. So far, 8 CN allergic patients are at the maintenance dose without relevant side effects. In contrast, 20 PN allergic children are already on maintenance dose, while 5 children discontinued OIT due to side effects. During OIT, minor reactions occurred in 17% of CN and 38% of PN allergic patients and included oral pruritus and abdominal pain. More severe reactions occurred in 5 (13%) PN allergic patients, with a grade 4 allergic reaction in 3 patients and suspicion of eosinophilic esophagitis in 2 patients. No severe reaction occurred in CN allergic patients.

Conclusion: OIT for CN and PN allergies in children is generally well tolerated, with CN OIT in particular being associated with only mild side effects.

P65

Outcomes of hospitalized solid organ transplant recipients with COVID-19 in the pre-Omicron and Omicron era

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Background: Observational data suggest that severity of disease with Omicron variant in general population is lower than with previous variants.

Aim: To compare the length of hospitalization and outcomes of COVID-19 infection in hospitalized solid organ transplant recipients (SOTR) in pre-Omicron and Omicron era at our centre.

Methods: SOTR with SARS CoV-2 infection hospitalized from March 2020 to April 2022 at our centre were divided in 2 groups; the pre-Omicron (preOm; March 2020 to December 2021) and Omicron (Om; January to April 2022) era. The patients' charts were reviewed for comorbidities, vaccination, treatment and outcomes of covid-19 infection.

Results: In preOm era 68 SOTR were hospitalized with COVID-19 and 31 in Om era; length of hospital stay was 15 (IQR 9-26) vs 11 (IQR 5-24) (p = 0.845) days; number of patients admitted to ICU due to critical COVID-19 was 10/68 (14.7%) vs 4/31 (12.9%) (p = 0.811) and mortality rate 5/68 (7.4%) vs 1/31 (3.2%) (p = 0.424), respectively. Patients were comparable regarding age, sex, type of transplanted organ, time since transplantation, comorbidities and immunosuppression. There were more vaccinated patients in the Om group with longer interval since last vaccine dose. Patients in the preOm group were treated more often with methylprednisolon and convalescent plasma, while in Om group treatment with monoclonal antibodies was more common.

Conclusions: Despite vaccination and lower general severity of Omicron infection, COVID-19 was still an important cause of prolonged hospitalization and ICU admission of SOTR at our centre.

P66

LAD-I: a magnesium sensing deficiency?

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Leukocyte Adhesion Deficiency-I (LAD-I) is caused by autosomal recessive mutations in CD18, the β subunit of the integrin LFA-1. Phenotypically, mutations disrupt the adhesion of leukocytes via LFA-1. Although diagnosis relies on CD18 expression, some mutations do not alter CD18 expression. Besides, no mutations that abrogate CD11a expression, the α subunit, have been reported. Therefore, in some patients, the mechanisms undermining adhesion may be more subtle than the loss of LFA-1 in the leukocyte surface.

We have recently shown that LFA-1 requires extracellular magnesium (Mg^{2+}) to adopt its active state. Elicited by T cell activation, magnesium-sufficiency sensed via LFA-1 enhances immune synapse formation and signaling, translating to a superior performance of T cells. Here, we propose that a subset of LAD-I patients might be affected by a conditional defect in LFA-1 that exacerbates when Mg^{2+} is scarce.

To test this, we genetically engineered T cells to express LAD-I-associated LFA-1 variants. Using *in vitro* and *in vivo* approaches, we have generated new insights on how mutations modify the $Mg2^{+}$ threshold required for LFA-1 conformational changes and signalling, and hence T cell immune and metabolic functions – that may also affect infection and cancer immunity in mice harbouring LFA-1 variants.

Hypomagnesemia exacerbates the immune dysregulation in infection and cancer. New and precise insights on how it undermines im-

munity will help devise simple yet cost-effective $Mg2^+$-based interventions for PIDs and other less severe immune dysfunctions aggravated by $Mg2^+$ deficiency.

P67

A review of clinical trial data on the recombinant zoster vaccine

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Background:

The pivotal phase 3 ZOE-50 and ZOE-70 trials (ZOE trials) reported recombinant zoster vaccine (RZV) efficacy against herpes zoster (HZ) of >90% in adults aged ≥50 years.

Aims: We reviewed published clinical trial data on RZV following ZOE trials.

Methods: PubMed was searched for clinical trial data on RZV after 2015.

Results: 45 articles were deemed relevant for review, 7 reported RZV efficacy in older adults against HZ, post-herpetic neuralgia (PHN), and non-PHN complications. RZV efficacy and safety were confirmed in subjects with frailty or with pre-existing potentially immune-mediated diseases and were shown to be unaffected by geographic region or ethnicity. Cross-over vaccination of individuals from placebo arms of the ZOE trials confirmed the safety profile. RZV safety and immunogenicity profile was not affected in individuals with prior HZ, those with prior live-zoster vaccine administration and in those with co-administration of other vaccines. Among adults from age 50, RZV immunogenicity was maintained for at least 10 years and efficacy to >84% annually, based on interim data up to year 8 post-vaccination.

Patient-reported outcome studies confirmed that RZV prevented quality of life deterioration by preventing HZ or by reducing its severity also in immunocompromised individuals.

Conclusion: The review demonstrates that RZV immunogenicity and efficacy are maintained in a broad range of populations and conditions and sustain over time. RZV safety profile appears clinically acceptable across those populations.

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P68

Treosulfan-based reduced-intensity allogeneic hematopoietic cell transplantation in adults with primary immunodeficiency: a case series

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Backgound: Primary immunodeficiencies (PID), are a rapidly expanding group of >500 genetically determined defects of immunity manifesting with increased susceptibility to infection, inflammation, autoimmune disease, lymphoproliferation, allergy, and malignancy. While initially mainly diagnosed in children, manifestations in adults are increasingly recognized. Apart from gene therapy, used in selected monogenic PIDs but far from being readily available, allogeneic hematopoietic cell transplantation (allo-HCT) is the only curative therapy.

Methods: We report on three adult patients with PID treated with reduced-intensity allogenic hematopoietic cell transplantation (HCT) with fludarabine/treosulfan conditioning and GvHD prophylaxis with alemtuzumab and a calcineurin inhibitor.

Results: Patient 1, a 51-year-old male, had common variable immunodeficiency (CVID) with protein-losing enteropathy. Patient 2 is a 29-year-old woman with STAT3 (signal transducer and activator of transcription 3)-dependent hyper-IgE syndrome (HIES), and patient 3 a 25-year-old male with XIAP (X-linked inhibitor of apoptosis)-deficiency presenting as treatment-refractory granulomatous enteropathy. All three patients engrafted and had 100% donor chimerism in blood. Two patients are alive and the patient with CVID died due to infection.

Conclusions: This series highlights issues of transplantation for PID in adults and treosulfan-based conditioning, feasible in PID patients with infectious complications being the major issue of concern.

P69

"Investigating the function of coronin proteins in immune cells: redundancy or cooperation?"

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T lymphocytes constitute an important part of the immune system: therefore, it is crucial to maintain homeostatic numbers of T cells to guarantee a continuous response to pathogenic triggers. The mammalian protein coronin 1 has been described to play a central role in T cell homeostasis. Deletion or mutation of coronin 1 in mice and humans results in profound peripheral T cell deficiency. Coronin 1 is a member of a family of 7 mammalian proteins, evolutionarily conserved from yeast to humans. We have analyzed the possible contribution of other members of the coronin protein family, and results will be presented dissecting the role of such coronin protein family members in T cell homeostasis.

P70

Manufacturing of memory stem cell-enriched T-cell products for clinical application

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In recent years, T-cell therapy for treatment of viral infections and hematological malignancies was introduced into clinics. However, manufacturing is often labour-intensive and translation of novel experimental research to clinical application is challenging.

Assuming that early differentiated T memory stem cells (Tscm) might improve patient outcome due to their longevity and robust proliferative potential, the aim of this project was to develop a good manufacturing practice (GMP)-compliant, closed, semi-automated process for manufacturing of Tscm-enriched virus-specific T cells for clinical application.

We upscaled T-cell expansion and introduced closed, automated devices for isolation of peripheral blood mononuclear cells (PBMC), T-cell expansion and cell harvest.

PBMC isolation was successfully performed on the automated CliniMACS Prodigy® device in a closed system with sufficient cell recovery and viability ($4.1x10^8$ PBMC from 400ml peripheral blood, viability 99%). Large numbers of virus-specific Tscm-enriched T cells could be expanded in G-Rex® 100 devices ($4.5\text{-}8.4x10^8$ cells; 77-424-fold increase of virus-specific T cells; 3.6-27% Tscm). Cell harvest with a Lovo® cell processing device allowed automated cell harvest, washing and final formulation of the product in a closed system.

Manufacturing of GMP-compliant Tscm-enriched T cells is feasible within semi-automated closed processes. This can have wide implications not only for virus-specific T-cell therapies but also for other cellular therapies such as treatment with genetically-modified T cells.

P71

Septic arthritis due to atypical organisms in the immune compromised host (ICH) – a report of two cases

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We discuss challenges in diagnosis and treatment of two cases with musculoskeletal infection.

Case 1. 17-year-old with AML with candidemia, mNGS(Karius) and Blood culture positive for *Candida parapsilosis* necessitating liposomal amphotericin and prolonged micafungin. MRI for leg pain revealed multifocal bilateral osteomyelitis and myositis. 3 months later, on antifungals, developed R knee arthritis. Synovial fluid positive for pan sensitive *C parapsilosis*. Two I&Ds, intra-articular micafungin and IV Caspofungin with no sterilization until repeat IV liposomal amphotericin and prolonged fluconazole. Awaiting BMT.

Case 2. 22-year-old with APDS (maternally inherited PIK3R1 gene mutation) CVID, generalized adenopathy, AHA, splenectomized and on IgG infusions, valganciclovir, TMP/SMX, penicillin, rituximab. Pelvic adenopathy caused L leg edema and ureteral obstruction. Cultures negative on pelvic lymph node biopsy with low copies by mNGS (?contaminant) and positive by 16srRNA for *Mycoplasma salivarum*.. Rituximab replaced by Sirolimus. MRI after 3 months showed myositis and bilateral knee effusions; synovial fluid negative cultures but positive for *Mycoplasma salivarum* on the 16srRNA PCR. Doxycycline provided sustained resolution.

Discussion: In case 1 the patient with refractory leukemia and *Candida parapsilosis*, had a protracted course despite antifungal and surgical therapy. In case 2, *Mycoplasma salivarium* was the.causative organism of septic arthritis. Molecular testing was useful as these organisms are persistent & difficult to culture.

P72

The cellular metabolism of SLE NK cells is primarily altered at the level of mitochondrial respiration

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Introduction: Systemic lupus erythematosus (SLE) is an inflammatory disorder of unknown origin. Natural killer (NK) cells are decreased and dysfunctional in SLE. Here, we examined the immunometabolic alterations of SLE NK cells.

Methods: SLE and healthy NK cells were isolated from human PBMCs. Glycolysis and mitochondrial respiration (OXPHOS) were measured using XFe96 Seahorse Analyzer. Mitochondrial function (membrane potential, mitochondrial mass), superoxide levels and lysosomes acidification were assessed by flow cytometry. Mitochondrial membrane potential and mass were analyzed by confocal microscopy (CM). Mitochondrial DNA was quantified by qPCR. Mitochondrial structure was examined by electron microscopy (EM).

Results: SLE NK cells exhibited increased OXPHOS, while their glycolysis was comparable to healthy NK cells. Mitochondrial mass is increased, while mitochondrial activity is decreased in SLE NK cells. Mitochondria from SLE NK cells displayed increased superoxide levels and elevated lysosomal acidification. Analysis of SLE NK cells by CM together with qPCR, confirmed an increased in mitochondrial mass, compared to healthy NK cells. Moreover, EM examination of mitochondria in SLE NK cells showed cristae disorganization.

Conclusion: SLE NK cells exhibit impaired OXPHOS, related to an accumulation of dysfunctional mitochondria, which show a profound alteration in their ultrastructure. These results suggest an alteration in the mitophagy of SLE NK and represent a major feature of SLE pathogenesis.

P73

Urinary tract infections and urine interleukine 17 levels in kidney allograft recipients- preliminary study

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Background: Interleukin 17 (IL17) represents significant mechanism of antibacterial immunity. Urinary tract infections (UTI) are recognized as a major clinical complication in kidney allograft recipients. Little is known about the role of IL17/23 axis in post-transplant immunity.

Purpose: To investigate the impact of UTI history on urine IL17 levels in kidney recipients.

Methods: 208 urine samples obtained from 135 kidney recipients, 1-240 months post-transplant were analyzed; 87 samples followed UTI history. IL17 levels were measured with ELISA and IL17/creatinine ratios were calculated. Machine learning algorithms and predictive models were implemented. Results: The values of IL17/creatinine ratio appeared varied (undetectable-12850pg/g). Post-transplant time point and the number of UTI episodes distinguished between undetectable, below median and over median levels. Higher prevalence of undetectable IL17 levels was found in samples obtained below 1,5 and after 194 months post-transplant, also in samples following single UTI episode (p = 0,02). Predictive models revealed and increasing trend in IL17 levels following both single and recurrent UTI up to 30 months post-transplant, both in males and females. No clear trends were observed in the samples obtained from individuals without UTI history in an analogous post-transplant timeframe.

Conclusions: Urine IL17 was frequently undetectable in the early and late post-transplant period. Detectable levels increased within first 30 months post-transplant in samples which followed UTI episodes, both in males and females.

P74

Development of a human in vitro lymphoid tissue model to study B cell responses

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Background: Humoral immune responses evolve from activated B cells in secondary lymphoid organs resulting in high-affinity antibodies against the priming antigen. Both *in vitro* immune assays – based on peripheral blood lymphocytes – and *in vivo* mouse models do not fully recapitulate human adaptative immunity.

Objectives: We aim at developing a human *in vitro* model of a secondary lymphoid organ to study B cell response.

Methods: *In vitro* culturing of human tonsil tissue explants in a perfusion (3D bioreactor) *vs* static system for 5d and 14d. Antigen specific (influenza vaccine) and unspecific stimuli (CpG, TRL ligand) were used to assess immune function. The systems were characterized by multicolor flow cytometry, multiplexed cross-binding immunoassays, histology (H&E) and immunohistochemistry.

Results: We assessed eleven tonsil explants. Both perfusion and static system could support the culture of tonsil explants overtime and the generation of B cell response upon stimulation. The perfusion system provided relevant advantages compared to the static one: (i) higher viability and cell density particularly at day 14; (ii) a more pronounced transition to pre-GC phenotype and plasmablast differentiation and higher influenza-specific antibody production after stimulation; (iii) a better maintenance of cell density and immunological architecture.

Conclusion: These results indicate that perfusion-cultured tonsil tissue could be a valuable human *in vitro* model for immunology research with application in vaccine research and in testing of immunomodulatory drugs.

P75

Immunocompromised patients with resistant HSV infections: the international early access program of pritelivir

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Background: HSV infections persist lifelong and carry the risk of serious complications in immunocompromised patients. Patients whose HSV is resistant to acyclovir and foscarnet or cannot tolerate foscarnet have limited treatment options. Pritelivir is a helicase-primase inhibitor that is currently in a Phase 3 trial in immunocompromised patients with acyclovir-resistant HSV infections.

Aims: To provide access to pritelivir through an Early Access Program (EAP) for patients ineligible for trials or registered treatment options.

Methods: We analyzed demographics, medical history, safety, and treatment patterns for all patients in the global EAP from Feb 2020 to May 2022.

Results: A total of 75 requests from 11 countries across Europe, Northern America, Africa, and Australia were received. Forty-four patients from 9 countries subsequently initiated treatment.

The main underlying causes for the immunocompromised state were transplant (57%) and HIV/AIDS infection (25%). In addition to acyclovir/foscarnet, 66% of patients had already received one or more off-label therapies (e.g. imiquimod (50%), cidofovir (25%), ganciclovir (7%)) prior to starting pritelivir.

Zero (0) Treatment Related SAEs were reported. Unlike in the Phase 3 trial, patients were allowed to initiate multiple treatment rounds to treat lesion recurrences. 34% of patients started multiple treatment rounds.

Conclusions: The high participation rate in the EAP highlights the unmet need in this patient population. Treatment was well-tolerated and successfully re-initiated. Further studies will assess outcomes of pritelivir therapy.

P76

Distinct subsets of CD4+ and CD8+ T cells in patients with squamous cell carcinoma

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Background: Effective antitumor immune response depends on the orchestration of T cell responses against squamous cell carcinoma (SCC). CD4+ and $CD8^+$ T cells play distinct roles in the regulation of the antitumor immune response via the production of cytokines, and the function of each T cell subset is controlled by specific master transcription factors. While efforts have been made to determinate how transcription factors modulate T cell responses in infection and autoimmunity, the roles of theses proteins in tumor immunity is less clear.

Purpose: Here we aimed to analyze the pattern of transcription factor and cytokine expression in $CD4^+$ and $CD8^+$ T cells from peripheral blood from SCC patients.

Methods: We investigated the phenotype of T cells in peripheral blood of patients with squamous cell carcinoma using four-color flow cytometry.

Results: We demonstrated that $ROR\gamma^+CD8^+$ T cells were increased in SCC patients compared with healthy donors, while T-bet and GATA-3 were expressed at similar frequency. The prevalence of $T\text{-}bet^+$, $GATA3^+$ and $CCR3^+CD4^+$ T cells was decreased in SCC patients. The majority of cytokine-secreting $CD4^+$ T cells were $IL4^+$, while IFN-γ, IL-4 and IL-10 were expressed at major frequencies by $CD8^+$ T cells in SCC patients.

Conclusion: Our findings showed decreased frequencies of Th1 T-cell populations and $CCR3^+CD4^+$ T -cell populations in the peripheral blood of SSC patients.

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P77

Atopy as an independent predictor for long-term patient and graft survival after kidney transplantation

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Background: Atopy is a genetic condition predisposing individuals to develop immunoglobulin E (IgE) against common inhaled allergens through T-helper 2 polarization mechanisms. The impact of atopy on graft survival in solid organ transplantation is unknown.

Methodology: We retrospectively analyzed 268 renal allograft recipients from the Swiss Transplant Cohort Study, a prospective multicenter cohort studying patients after solid organ transplantation, with a 9-year median follow-up (IQR 3.0). We used the Phadiatop assay to measure IgE antibodies against a mixture of common inhaled allergens to identify pre-transplantation atopic patients (>0.35 KU/L).

Results: Of 268 kidney transplant recipients, 66 individuals were atopic (24.6%). Atopic patients were significantly younger than non-atopic patients (49.6 vs 58.0 years old, P = 0.002). Patient and graft survival at ten years of follow-up were significantly better in the atopic group, 95.2% versus 69.2% patient survival (P <0.001), and 87.9% versus 60.8% graft survival (P <0.001), respectively. A multivariate Cox analysis revealed that atopy predicted recipient and graft survival independently of age and living donor donation. Finally, we found similar rates of biopsy-proven acute cellular and antibody-mediated rejections between atopic and non-atopic recipients.

Conclusion: Atopy was associated with better long-term patient and graft survival, independently of age and living donor donation after kidney transplantation. Yet, atopy should not be used as a predictor for acute rejection.

P78

Predictors of mortality in neutropenic enterocolitis among children and young adults with acute myeloid leukemia in low middle income countries

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Background: Neutropenic enterocolitis (NEC) is a life-threatening disease with substantial morbidity and mortality, seen primarily in patients with hematologic malignancies.

Methods: This was a retrospective study at the National Cancer Institute, Cairo University. The computerized records were screened for ultrasound or computerized tomographic scan requests for abdominal pain for all Acute myeloid pediatric inpatients (2012-2016). clinical data for patients with features of NEC and D 30 Mortality was reported.

Results: The incidence of NEC among our inpatients was 24% (49/203). Most (93%) patients were profoundly neutropenic (ANC <100). All of them needed ICU admission. Three patients had laparotomy, and 2 out of 3 cases who had Laparotomy was diagnosed with Mucormycosis. 30-Days mortality was 44.8% (22/49). Relapsing Typhlitis in subsequent courses was observed in 6/27 (22%) patients. Fulminant gram-negative sepsis without surgical intervention was the leading cause of death. NEC-related mortality was significantly higher among patients receiving high-risk protocol with more intensive chemotherapy and in patients with Co-Morbidities (P-value of 0.005 and 0.037 respectively). Also, mortality was increased among patients with more than 2 presenting clinical symptoms with a P-value of 0.01.

Conclusion: Although surgical intervention should be reserved for specific complications, its delay increases the incidence of NEC-

related mortality. Fungal infection should be suspected especially in cases with worsening signs of typhlitis despite broad antimicrobial coverage.

P79

The use of cytomegalovirus (CMV) T cell immunity panel to assess the risk of CMV infection in recipients of cellular therapy with low level CMV viremia

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Background: Due to the risk CMV infection poses to Hematopoietic cell transplant (HCT) and Chimeric antigen receptor (CAR) T cell recipients, a better approach is needed to support the initiation of antiviral therapy and/or secondary prophylaxis without relying solely on an arbitrary CMV viral load thresholds. The use of CMV specific T cell assays such as the CMV T Cell immunity panel (CMV-TCIP) may identify patients at high risk for CMV reactivation and predict progression from low level viremia to clinically significant CMVi (CS-CMVi). Our objective was to identify HCT and CAR T cell recipients with low level CMV viremia who are at high risk for CS-CMVi with the use of CMV-TCIP while on or off letermovir for CMV prophylaxis.

Methods: We performed a prospective observational cohort study where we enrolled adults (≥ 18 years) HCT and CAR T cell recipients with CMV viral load of <1000 IU/ml (or <500 IU/ml for high risk patients) within a year of cellular therapy. Patients were stratified into 2 arms based on the use of letermovir for prophylaxis; CAR T cell recipients were enrolled in the non letermovir arm. CMV-TCIP assay was performed at Eurofins-Viracor laboratory at baseline, once a week for 4 weeks, and once every other week for 1 month. A cutoff of ≥ 0.20 % for CMV specific CD4 and CD8 activity was considered a good response based on prior studies. If results at baseline (week 0) were unavailable, results from week 1 or 2 were used. Outcomes of interest included CS-CMVi at 2 months, and relapse and all-cause mortality at 2 and 6 months from enrollment.

Results: Out of the 65 patients enrolled, 57 (88%) underwent an HCT, with most patients receiving a transplant from a match related (MRD) or unrelated donors (MUD). On univariate analysis, progression to CS-CMVi while off letermovir was more common in patients with a poor than good CMV T cell responses (40% vs 0%; $p = 0.0362$). Patients with poor CMV specific CD4 responses had higher peak CMV viral load and more CS-CMVi regardless of being on letermovir. At 6 months of follow-up, patients with poor CMV specific T cell responses had higher all-cause mortality ($p = 0.0316$) and trend towards a higher relapse of their underlying malignancies ($p = 0.070$) when compared to patients with good CMV specific T cell response.

Conclusion: Our results demonstrate that poor CMV specific T cell function can be associated with CS-CMVi and 6 months all-cause mortality.

P80

Basophil activation tests with cryopreserved mRNA-based COVID-19 vaccines

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Background: The management and mechanisms involved in allergies to mRNA anti-SARS Cov2 vaccines remain debated. The availability of mRNA vaccines limits their use for Basophil Activation Test (BAT). Cryopreservation of mRNA vaccines from leftover doses or vials may help standardize this assay better.

Methods: Individuals with respectively negative (n = 10) and positive (n = 10) skin testing for mRNA vaccines were included in this study. CD63 upregulation in basophils was compared using fresh leftover or cryopreserved mRNA vaccines from Pfizer BioNTech (BNT162b2) and Moderna (mRNA-1273). Spike protein expression was used as a surrogate marker for the evaluation of mRNA vaccine's function *in vitro*.

Results: CD63 upregulation in basophils was significantly higher in patients with positive intradermal skin testing (IDR) with both mRNA vaccines. A significant correlation was found comparing (1) fresh BNT162b2 and mRNA-1273 vaccines, (2) cryopreserved and fresh BNT162b2 vaccines, (3) cryopreserved and fresh mRNA-1273 vaccines, and (4) cryopreserved BNT162b2 and mRNA-1273 vaccines. Importantly, CD63 upregulation in basophils was independent of the capacity of the mRNA vaccines to induce spike expression.

Conclusions: BAT performed with mRNA vaccines can be used as IDR surrogates to identify COVID-19 mRNA vaccine-sensitized individuals. These mRNA vaccines can be safely cryopreserved for BAT assays independently of their *in vitro* function. The current findings will allow broader use of mRNA vaccines for diagnostic tests and research purposes.

P81

Th9 cells depend on cystine uptake and PPAR-γ signaling to prevent unchecked lipid ROS and cell death

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Background: Pathogenic T_H2 cells (pT_H2) are key mediators of type-2-driven skin disease. Current treatments inhibit the activation of pT_H2 cells or neutralize their effector molecules. Yet, therapies targeting the survival of pT_H2 cells in the skin are missing. T_H9 cells are IL-9-expressing T_H cells that share overlapping features with pT_H2.

Aim: A better characterization of the T_H9 subset is of utmost importance to identify regulators of cell survival that are specifically expressed by these cells and that might represent novel therapeutic targets.

Methods: Given the specific expression of PPAR-γ in T_H9 cells, we explored the effect of its inhibition on cellular survival and function to evaluate its value as therapeutic target.

Results: Inhibition of PPAR-γ in T_H9 cells downregulated SLC7A8 (LAT2), a transporter of neutral amino acids, while inducing compensatory upregulation of SLC7A11, a cystine-glutamate antiporter, suggesting a specific need for cystine in T_H9 cells. Indeed, cystine-starvation or inhibition of SLC7A11 induced lipid-peroxidation, cell death and bioenergetic failure in T_H9 cells that was exacerbated by PPAR-γ inhibition. In an ex-vivo model of allergic contact dermatitis, combined SLC7A11 and PPAR-γ inhibition selectively depleted T_H9 cells.

Conclusion: These data indicate that PPAR-γ is a regulator of amino acids-metabolism in human T_H9 cells, which depend on cystine for control of lipid peroxidation and bioenergetic homeostasis. Interference with cystine metabolism or PPAR-γ might open up therapeutic avenues to deplete pT_H2 cells in immunopathology.

P82

Testing for genuine T cell immune responses to SARS-CoV-2 in patients with common variable immunodeficiency or B cell depletion

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Background: Immunodeficient (ID) patients are among risk groups for severe disease after SARS-CoV2 (CoV2) infection. Despite high population immunity, ID patients remain difficult to medically advice due to their impaired immunity during an evolving CoV2 strains pandemic.

Aim: We examined if durable immunisation to CoV2 infection or vaccination is developed. Serology cannot answer this since IgG replacement therapy now contains CoV2 antibodies. Instead, a cellular diagnostic test for patients' CoV2 memory T cells was used.

Methods: We included 13 ID patients (aged 34–78; 7 female) who were vaccinated against CoV2 or previously infected: 5 with common variable immunodeficiency (CVID) and 8 with B cell deficiency (BCD) due to anti-CD20 or BTK inhibition therapy. Peripheral blood mononuclear cells isolated from whole blood were cultured with CoV2 spike protein or peptides for 7 days, then measured for T cell activation markers by flow cytometry.

Results: CoV2 spike specific CD4 or CD8 T cells were detectable in 7/8 BCD and all CVID patients. However, only 3/5 CVID and 6/8 BCD patients had both CD4 and CD8 T cell responses.

Conclusion: Genuine CoV2 T cell responses are detectable with a cellular diagnostic test in CVID and BCD patients after immunisation. As ID patients are heterogenous, a diagnostic test for memory T cells against CoV2 gives clinicians evidence of a patient's own immune response beyond passive IgG replacement therapy. This aids in consulting advice for infection avoidance strategies and indication for urgent treatment with monoclonal antibodies against CoV2.

P83

High levels of monocytic myeloid-derived suppressor cells are associated with favorable outcome in patients with pneumosepsis and multi-organ failure

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Background: Monocytic and PMN myeloid derived suppressor cells (M-MDSCs and PMN-MDSCs) are myeloid cells with immunosuppressive functions. MDSCs have been associated with poor outcome in sepsis patients. However, sepsis patients exhibit signs of inflammation and immunosuppression.

Aim: To analyze MDSCs in critically ill sepsis patients with high likelihood of death.

Methods: This was a prospective observational cohort study in 8 ICUs in Greece, enrolling critically ill patients with pneumosepsis and multi-organ dysfunctions. Blood was collected at study inclusion to detect MDSCs by flow cytometry and unsupervised clustering of leukocyte populations.

Results: Forty-eight patients were included, 34 died within 90 days. M-MDSCs and PMN-MDSCs were increased 3-10 fold in sepsis patients ($P < 10^{-4}$). High PMN-MDSCs were associated with secondary infections and new sepsis episodes ($P < 0.05$). M-MDSCs were more abundant in survivors than in deaths ($P = 0.03$). Stratification revealed that high levels of M-MDSC were associated with reduced 90-day mortality ($P = 0.003$, HR = 3.2, 95%CI: 1.4-7.2). Combining high M-MDSC levels with low APACHE II score improved stratification ($M\text{-MDSCs}^{high}$/APACHE II^{low} vs $M\text{-MDSCs}^{low}$/APACHE II^{low}: 20% vs 80% 90-day mortality, $P = 0.0096$, HR = 7.2, 95%CI: 1.6-32). M-MDSCs remained correlated with mortality in in multivariate analyses.

Conclusions: This is the first study to associate high levels of M-MDSCs with improved survival in sepsis patients. MDSCs might be prognostic or theragnostic biomarkers in sepsis.

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P84

Rapid increase of myeloid-derived suppressor cells and prolonged innate immune dysfunctions in patients with COVID-19

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Background: PMN and monocytic myeloid-derived suppressor cells (PMN-MDSCs, M-MDSCs) are immunosuppressive cells rising during infections.

Aim: To characterize the dynamic of MDSCs in relation with immune parameters in COVID-19 patients followed for 3 months.

Methods: 56 SARS-CoV-2 infected adult patients hospitalized at CHUV were included. Blood was obtained at inclusion and 3 months later in 21 patients, and from 10 healthy controls. Blood was stimulated with TLR ligands. Leukocyte populations and cytokines were analyzed by flow cytometry, mass cytometry, multiplex bead assay and ELISA.

Results: At hospital admission, PMN-MDSCs and M-MDSCs were increased 2-4-fold in COVID-19 patients ($P < 0.05$). PMN-MDSCs and M-MDSCs counts were higher in severe than in moderate COVID-19 patients ($P < 0.005$). PMN-MDSCs and M-MDSCs correlated positively with EGF and HGF ($P < 0.05$). M-MDSCs correlated positively with IL-1β, IL-7, PDGF and VEGF ($P < 0.05$). In whole blood stimulated with TLR ligands, the proportion of TNF and IL-6-producing monocytes and DCs were reduced in patients. After 32 months, MDSCs were back to normal levels, while the production of cytokines by blood, monocytes and DCs was still largely affected.

Conclusions: PMN-MDSCs and M-MDSCs were elevated and correlated with disease severity in patients analyzed at hospitalization. Innate immune blood responses were impaired in patients, which persisted for up to 3 months. Our results suggest that COVID-19 induces rapid and long-standing innate immune dysregulation.

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P85

Trained immunity provides durable protection against deadly sepsis

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Background. Trained immunity reflects the fact that the innate immune system adapts to a challenge to mount an improved response to a secondary challenge. We reported that trained immunity protects mice from peritonitis, systemic infection, enteritis and pneumonia, and demonstrated intergenerational transmission of trained immunity protecting from infection.

Aim: To determine whether trained immunity confers prolonged protection from bacterial infections.

Methods: Mice were trained and challenged 1 week to 7 months later with Escherichia coli i.p. or Listeria monocytogenes i.v. Organs were collected to quantify leukocytes and bacteria, and to measure the antimicrobial activity of leukocytes.

Results: Training induced an accumulation of small peritoneal macrophages that persisted 3 months. Peritoneal cells collected 7 months after training produced increased IL-6 ($P < 0.01$). Training increased blood monocytes and PMNs. Numbers decreased after 3 months and returned to normal after 7 months. Blood collected 3 months after training controlled the growth of Listeria and produced more cytokines than control blood ($P < 0.05$). In the model of E. coli peritonitis, mice trained 7 months earlier showed reduced bacteremia ($P = 0.04$) and increased survival (P 0.056). In the model of systemic listeriosis, mice trained 3 and 7 months earlier showed decreased bacteremia ($P < 0.05$) and increased survival ($P = 0.002$ and 0.08).

Conclusions: Training has long-term effects on innate immune cell number and reactivity, and mediates long-lasting protection against lethal infections.

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P86

Transmission of trained immunity and heterologous resistance to infections across generations

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Background: Trained immunity refers to the capacity of the innate immune system to recall an initial challenge to mount an improved response to a secondary challenge. Trained immunity is not antigen specific. Accordingly, we reported that trained immunity confers broad-spectrum protection against bacterial infections. Intergenerational inheritance of immune traits linked to epigenetic modifications has been demonstrated in plants and invertebrates.

Aim: To define whether trained immunity is transmissible through generations in a mammals.

Methods: Male or female mice were trained. Naïve mice were crossed with resting or trained mice to obtain resting (control) F1R mice or trained F1T mice. F1 mice were challenged with *Listeria monocytogenes* i.v. Sperm and blood were collected to quantify bacteria, leukocytes and to define sperm methylome.

Results: F1R mice all died from listeriosis. F1T females and F1 males obtained by crossing trained females with resting males as well as F1T males obtained by crossing trained males with resting females showed increased survival (P = 0.04 – <10e-3). Accordingly, F1T mice showed reduced weight loss and bacteremia 24/48h post-infection (P = 0.05 – <10e-3). PMNs and Ly6Ghigh monocytes were increased in blood of F1T mice. Sperm DNA of parental male mice infected with *C. albicans* revealed training-dependent DNA methylation differences linked to immune gene loci.

Discussion: These results provide evidence for inheritance of trained immunity in mammals, enhancing protection against infections.

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P87

Voriconazole versus amphotericin B for empirical antifungal therapy in hematologic patients with febrile neutropenia: a randomized controlled trial

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Background: Amphotericin B deoxycholate (AMBd) has been routinely used for empirical treatment of invasive fungal diseases (IFD) in febrile neutropenia (FN) in resource-limited countries. The efficacy of voriconazole (VOR) for empirical treatment in FN patients is not well studied.

Aims: To compare the efficacy and safety of VOR versus AMBd for empirical antifungal treatment in FN patients

Methods: An open-labelled, randomized controlled trial was conducted. Hematological patients with FN were randomly enrolled into VOR or AMBd group. The primary outcome was 28-day IFD-free survival. The secondary outcomes were adverse drug reactions, length of hospital stay, and rate of antifungal switching.

Results: 38 patients were enrolled. The mean age was 43.6 year and 57.9% was male. Twenty-one patients were assigned to VOR and 17 patients to AMBd. Baseline characteristics were comparable, in which AML was the most common (65.8%). All participants were high-risk (MASCC <21). 28-day IFD-free survival in AMBd and VOR arm were 44.8% and 55.3%, respectively (p = 0.577). Participants in AMBd group had a higher rate of antifungal switching (52.9% vs. 0% in AMBd and VOR group, respectively; p <0.01). Greater adverse effects were observed in AMBd than VOR group (100% vs. 47.6%; p <0.01). The most common adverse effect in AMBd group was hypokalemia (82.4%). The mean length of hospital stay was not different between the two groups.

Conclusions: VOR is as effective as AMBd for empirical antifungal therapy in FN hematological patients with fewer adverse effects and antifungal drug switching.

P88

Clinical outcome in children with cancer, fever and neutropenia, with polymicrobial bloodstream infections

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Background: The clinical relevance of the finding of polymicrobial bloodstream infections (BSI) in episodes of fever and neutropenia (FN) in children with cancer has not been established. The aim of this study was to evaluate the clinical outcome in children with cancer, presenting episodes of FN with polymicrobial BSI.

Methods: Children admitted with episodes of high-risk FN in 6 public hospitals in Santiago, Chile, were monitored throughout their clinical course for occurrence of BSI. We compared the clinical outcome of children with polymicrobial BSI versus those with single agent isolation.

Results: A total of 1074 episodes of high-risk FN were enrolled between 2016 and 2021 in any of the six participating hospitals, of which 27% (298) had positive blood cultures and 3% (32) had polymicrobial BSI. The most frequent identified agents were Viridans group streptococci (20%) and Escherichia coli i(19%), followed by Coagulase negative staphylococci in 14%. Children with polymicrobial BSI presented more days of fever (7 versus 4 days, p = 0.02), needed longer courses of antimicrobial therapy (16 versus 14 days, p = 0.04) and had higher mortality at day 30 (13% versus 1%, p = 0.003). Conclusions: Children with cancer and FN with polymicrobial BSI had a more adverse clinical outcome than children with single agent isolation BSI. Our results suggest the necessity to improve the microbiological diagnosis for an optimal detection of multiple microorganisms in episodes of high-risk FN, in order to contribute to a more timely and rational use of antimicrobials in this population.

P89

Importance of standardized drug allergy documentation: analysis of allergy alerts in patients hospitalized in a tertiary health center in Switzerland

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Background: Adverse drug reactions are an important cause of in-hospital morbidity, with drug hypersensitivity (DH) accounting for 10% of fatal cases. Most hospitals use electronic health records (EHR) to warn of DH. Indiscriminate DH history taking bloats the alert system and leads to unjustified drug avoidance. For example, unfounded restriction of beta-lactams (BL) as 1st-line antibiotics increases health costs and antimicrobial resistance.

Aim: To assess the quantity and quality of DH documented in EHR of Lausanne Hospital (CHUV).

Methods: Retrospective study on patients admitted to CHUV for ≥24h between 2010—2021. Data on allergy alerts, age, gender were obtained after ethics approval (2021-01784).

Results: Of 192'444 patients (hosp. on average 3 times), 16% had allergy alerts. They were more often females and older than those without allergies. DH constituted 60% of all alerts, mainly to BL (30%), NSAID (8%) and ICM (7%). DH reactions were mostly limited to the skin (50%), anaphylaxis in rare cases (6%). Of patients

deemed allergic to BL antibiotics, 16% had specific culprits, while all others were tagged as 'penicillin allergic'. DH merely based on patient history or subject to specialist's work-up were indistinguishable.

Conclusions: Reliable data on DH (type and severity of reaction, prime culprit) is difficult to obtain, as highlighted by our study. Better documentation coupled with specialized work-up could improve patient safety and reduce health costs. As a first step, we propose to differentiate EHR alerts in 'history of DH' and 'DH confirmed by work-up'.

P90

Predicting the risk of cytokine release syndrome induced by cancer immunotherapies using mechanistic modelling and risk factors learnt from Covid-19

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Background: Cancer immunotherapies such as CAR-T-cells or bispecific antibodies can induce over-activation of the immune system, leading to Cytokine Release Syndrome (CRS). The risk for CRS can be dose-limiting in the application of cancer immunotherapies. Similarly, infections, such as Covid-19, can cause CRS by uncontrolled immunopathology.

Hypothesis: CRS immunopathogenesis is multifactorial and difficult to define. High IL-6 serum levels poorly predict the CRS severity. Quantitative integration of patient-specific factors to predict the individualized risk of developing CRS allows adapting the dosage of cancer-immunotherapeutics while minimizing adverse effects and, therefore, can improve the individual benefit-risk ratio and health outcomes for patients.

Methods: We mine large longitudinal health records of patients with CRS across multiple conditions to delineate risk factors of CRS. We integrate individualized CRS risk factors into a mathematical mechanistic model for CRS onset.

Results: Using a cohort of 39 000 Covid-induced CRS, we isolated CRS risk factors that align with risk factors of CRS during cancer immunotherapies. We developed a mechanistic model for cytokine dynamics and CRS onset during SARS-CoV2 infection or cancer immunotherapy. We run *in silico* trials on virtual patients and predict *in silico* the impact of individualized treatment on reducing adverse effects.

Conclusions: We show a proof of concept that risk factors predictive of CRS can be identified on large-scale patient datasets to predict individualized drug effects.

P91

Improved scRNA-seq bioinformatics removing high-rate coverage bias in BK Polyomavirus (BKPyV)-infected primary human kidney cells (RPTECs)

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Uncontrolled BKPyV-replication causes premature renal failure in 10%-20% of kidney transplant (KT) patients. Since antivirals are lacking, current treatment relies on screening for plasma BKPyV-DNAemia and reducing immunosuppression. To identify novel antiviral targets and markers of virus-induced host cell changes, we analyzed BKPyV-infected RPTECs at 24hpi and 48hpi by scRNA-seq using the 10x Genomics-3'kit. Reads covering the circular BKPyV-DNA genome mapped preferentially to early viral gene region (EVGR) at 24hpi and shifted to 100-fold higher levels in late viral gene region (LVGR) at 48hpi corresponding well to BKPyV-Dunlop protein expression by immunoblot and immunofluorescence. Besides novel splicing sites and circRNA, significant coverage inhomogeneities were identified at locations different than the terminal polyA-mRNA. Dominant inhomogeneities consisted of peaks / plateaus in non-coding control region and EVGR rather than LVGR originating from library preparation by: i) terminal template-switch-oligo (TSO)-priming without fragmentation and ii)-internal TSO-priming with or without fragmentation. Read coverage of the circular mitochondrial genome revealed similar inhomogeneities at two sites (D-Loop, ND3). Bioinformatic library curation using SoupX and two TSO-specific interventions removed inhomogeneities and improved identification of BKPyV-infected cells and associated cell transcripts. Our results will optimize scRNA-seq pipelines and identify robust changes of BKPyV-replication in renal cell culture and KT patient samples.

P92

Expansion of hepatic myeloid-derived suppressor cells in a carbon tetrachloride murine model of cirrhosis

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Background: Previously, we identified immunosuppressive M-MDSC in the circulation of patients with cirrhosis and liver failure. These cells increased with disease severity and were associated with distinct impaired innate and adaptive immune responses, increased infection susceptibility and mortality. Impaired immune responses and M-MDSC expansion were reversed by TLR3 agonism *in vitro*.

Aim: Identify MDSC in murine models of chronic liver injury and assess the safety and efficacy of poly(I:C) administration *in vivo*.

Methods: C57BL/6C mice were administered CCl_4 (0.4 ml/kg i.p.) for 6 weeks. To mimic acute insult, a group was injected LPS (i.p.) 24h prior to sacrifice. Poly(I:C) (1.6 mg/kg i.p.) was administered 4 times over 7 days prior to sacrifice in the CCl_4-only model. Cells from blood and livers were isolated and PMN- & M-MDSC were identified with flow cytometry. Effects on T cell proliferation and cytokine responses will be assessed. Histopathology of liver sections was evaluated on H&E stainings. Plasma ALT, bilirubin and albumin were quantified.

Results: Distinct PMN- & M-MDSC subsets expanded in the blood (2-fold) and liver (7-fold) of the CCl_4 model. An additional LPS injection further increased MDSC numbers. Both subsets of hepatic MDSC expressed markers Axl and Mertk, while M-MDSC expressed PD-L1. Poly(I:C) administration did not reduce MDSC numbers. Liver damage/function and histopathology were unvaried following poly(I:C) administration compared to controls.

Conclusions: We identified MDSC in the circulation and liver in two murine models of chronic liver injury.

P93

Intradermal skin test with mRNA vaccines as a surrogate marker of T cell immunity in immunosuppressed patients

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Background: The role of T cell immunity in protection against COVID-19 in immunosuppressed patients who failed to mount serological responses remains ill defined.

Hypothesis: Vaccine-based intradermal skin test (IDT) serves as a surrogate marker of T cell responses in seronegative immunosuppressed patients.

Methods: We compared anti-SARS-CoV-2 antibodies and cellular responses in vaccinated immunosuppressed (IS) patients (n = 58), healthy unvaccinated naive controls (NC, n = 8) and healthy vaccinated controls (VC, n = 32) by Luminex, IFN-γ ELIPSOT and IDT 3 to 6 months after vaccination. In 3 VC we performed a skin biopsy 24h after IDT and performed single-cell RNAseq of the skin-infiltrating $CD45^+$ cells.

Results: Seronegative NC had no detectable T cell responses and negative IDR, whereas VC had anti-SARS-CoV-2 antibodies (100%), positive ELIPSOT (90%) and IDR (90%). Overall IS patients had significantly less antibodies up to 39 weeks after vaccination compared to VC but similar ELIPSOT responses. ELISPOT was positive in 33.3 % and 66.6 % and IDR in 62.5% and 90.5% of seronegative vs seropositive IS patients respectively. Conversely, patients with negative IDR had significantly lower T cell responses and IgG titers than those with positive IDR. Importantly, the TCR repertoire of infiltrating skin lymphocytes revealed 18/1064 clonotypes with known specificities against SARS-CoV-2.

Conclusion: Our results indicate that local reaction to IDR is partially composed of SARS-CoV-2-specific T cells. IDR represents a promising tool to cost-effectively monitor SARS-CoV-2 specific T cell immunity in IS patients.

P94

Mapping the Toll-like receptor dependent activation of human microglia

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Microglia cells are a unique residential immunocompetent cell type of the central nervous system maintaining the homeostasis. Upon insults, microglia are the first and most rapidly activated cells through Toll-like receptors (TLR). The present study aims to generate footprints of various models of human microglia depending on specific TLR activation to predict TLR detection of neurotropic viruses. To this end, various models of human blood monocyte-derived microglia and human primary microglia were treated with specific ligands for TLR3, TLR7, TLR8 and TLR9. Zika virus was used as viral candidate. Transcriptomics analysis upon treatment with TLR ligands and Zika virus generated transcriptome footprints and identified soluble factors CCL2, CCL5, IL-6, IL-10, IL-17, IL-18, IL-23, IL-1β, TNF-α, TGF- α, TGF-β, PGRN, IFN-α, IL-1α, CCL20, CXCL1, CXCL9, CXCL10, CCL17, CCL22, CCL24, CSF-1 and cell surface makers CD206, CD14, CD32, CD163 for differential expression. Transcriptomics are validated by the generate of footprints for the soluble factors and phenotype markers candidates. For soluble factors, release of CCL2 and CCL5 was mostly regulated by all TLR ligands whereas IL-1β and IL-6 by TLR3 ligand preferentially. Phenotype of CX_3CR1^+ $CD11b^+$ microglia could be regulated by all TLR ligands for CD14 whereas CD206 was unaffected. However, discrepancies exist between the various human microglia models. Overall, pro- and anti-inflammatory markers were identified to generate footprints of transcriptome, soluble factors and phenotype.

P95

Ruxolitinib inhibits the proliferation of Epstein Barr virus (EBV)-specific T cells and limits their killing efficiency in vitro

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Signaling through Janus kinases (JAKs) and signal transducers and activators of transcription (STAT) contributes to inflammation and tissue damage in graft-versus-host disease (GVHD). Ruxolitinib is a selective inhibitor of JAK1 and JAK2 that is used for glucocorticoid-resistant GVHD. However, the use of ruxolitinib predisposes reactivation of viral infections. Impact of ruxolitinib on virus-specific T-cell properties and function are not well studied.

We used a protocol to rapidly expand EBV-specific T cells and co-cultured them one week with human lymphoblastoid cell lines (LCLs) and different ruxolitinib concentrations comparable to doses used in humans (0μM, 10 nM, 100 nM and 1 μM). *In vitro*, we found that ruxolitinib inhibits concentration-dependent the absolute EBV-specific T cell count, their proliferation and their cytotoxic capacity. With increasing ruxolitinib concentration, effector memory populations of EBV-specific T cells were enriched and exhaustion markers such as PD1 and TIGIT were down-regulated on EBV-specific T cells exposed to higher doses of ruxolitinib.

In summary, our results demonstrate how ruxolitinib negatively impacts the functionality of EBV-specific T cells. Further studies are needed to confirm the results in patients treated with ruxolitinib and to understand the durability of its effect.

P96

Burden of congenital cytomegalovirus among newborns/infants <2 years of age from 2010 to 2020

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Background: Congenital cytomegalovirus (cCMV) is the leading cause of congenital birth defects worldwide. 1 in 200 infants is born with cCMV and 10% exhibit symptoms at birth; long-term sequelae include sensorineural hearing loss and developmental delays. Without routine newborn surveillance, it is difficult to assess the true cCMV burden.

Aim: We describe the global epidemiologic burden of cCMV from 2010-2020 by performing a systematic literature review.

Methods: Publications on CMV-related epidemiologic burden were identified using Medline, Embase, and LILACS. Estimates of cCMV in at-risk age groups (newborns and infants) were extracted from studies published from 2010-2020, excluding systematic literature reviews, chart reviews, case series, and congress abstracts. The primary outcome was cCMV birth prevalence, defined by CMV polymerase chain reaction in saliva or urine samples.

Results: Of 8970 records on CMV epidemiologic burden across all ages, 3600 were screened. After excluding records, 21 reported cCMV infection in newborns/infants in 13 countries. cCMV birth prevalence ranged from 0.28%-1.30% among publications reporting on universal screening (n = 5); 0.6%-29.2% among publications reporting on targeted screening (n = 15); and 36.0% in 1 publication reporting on prenatal screening.

Conclusion: There is a lack of cCMV epidemiologic data worldwide, with inconsistent and varied newborn screening efforts. Implementation of consistent newborn screening methods is essential to accurately determine cCMV burden, justify future vaccine introduction, and measure impact.

P97

Rapid drug desensitization after anaphylaxis to chemotherapeutic agents in gynecologic tumors

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Background

Treatment with platin salts (PS) and taxanes (TX) is often associated with allergic and pseudoallergic hypersensitivity, limiting its use as standard therapy in gynecologic tumors. Rapid drug desensitization (RDD) can induce temporary tolerance and thus allows continuation of standard treatment.

Methods: Retrospective, descriptive analysis of allergy diagnostics and RDD outcome in patients with PS- or TX-induced reactions during chemotherapy of gynecologic cancers from 2012-2019.

Results: 54 patients (51 female, mean age 59±11 years) with mainly gynecologic tumors were included, 32/54 with hypersensitivity to TX and 22/54 to PS.

Skin tests (prick test; intradermal test) were performed with TX (6/29 of tested patients pos; 5/28 with paclitaxel, 1/17 with docetaxel) and

PS (9/28 of tested patients pos; 8/20 with carboplatin, 1/6 with cisplatin and 0/2 in oxaliplatin).

No association of skin test positivity with severity of the index reaction was seen. 47 RDD procedures were performed in 33 patients. RDD with TX was successful in 19/27 procedures, successful with modification of the protocol in 8/27 and unsuccessful in 0/27. RDD with PS was successful in 6/20, successful with modifications in 13/20 and unsuccessful in 1/20. Protocol modifications were needed after break-through reactions (BTR) during RDD and included therapeutic interventions to control the BTR and adaptions of the protocol.

Conclusion: In 97.9% of RDD, the entire dose of chemotherapy could be administered during RDD despite prior hypersensitivity to the drug. Skin test-positive patients had more BTR during RDD.

P98

Monocytes from squamous cell carcinoma patients promote proliferation and invasion of oral cancer cells

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Background: Monocytes are known to promote tumor initiation, progression and metastasis. Emerging evidence suggests that circulating monocytes show functional alterations in cancer. Purpose: Based on these observations, the aim of this study was to examine whether circulating monocytes from squamous cell carcinoma patients exhibit a protumor phenotype.

Methods: To explore this, we first characterized peripheral blood monocytes from squamous cell carcinoma (SCC) patients by flow cytometry. Monocytes were isolated, cultured and conditioned media (CM) was obtained. To examine whether the inflammatory medium derived from monocytes affect the invasion and proliferation of the SCC cell line (SCC-25), in vitro invasion and proliferation assays were performed.

Results: SCC patients had an increase in the frequency of non-classical monocytes and a significant decrease in the frequency of intermediate monocytes compared to healthy controls. Our findings show that monocyte-derived CM induced invasion and proliferation of SCC cell line. The proteome profile analysis revealed the up-regulation of amphiregulin (AREG), matrix metallopeptidase 3(MMP3) and Osteopontin (OPN) in SCC cell line exposed to monocyte-derived CM. Notably, the exposure of the SCC cell line to the monocyte-derived CM induced a switch between epithelial-like and mesenchymal-like phenotype, which facilitates in vitro invasiveness.

Conclusions: Our findings indicate that factors secreted by monocytes may influence the epithelial-mesenchymal transition of squamous cell carcinoma cancer cells and favors metastatic behavior. Financial support: FOB-USP, CNPq, PROEX-CAPES and FAPESP.

P99

Oral ibrexafungerp outcomes in patients with chronic mucocutaneous candidiasis (CMC)

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Background: *C. albicans* is the predominant organism causing CMC, manifest as esophageal/oropharyngeal candidiasis (EC/OPC) or skin/nail disease. Infections arise from colonized patients (pts) who are predisposed with innate or secondary immune deficiency. CMC pts usually are treated with oral azoles. When pts are unresponsive/intolerant to azoles, there are limited treatments, usually IV. Oral ibrexafungerp (IBX) is a triterpenoid with MOA similar to echinocandins (glucan synthase inhibition). Its activity includes *Candida* spp, including azole+echinocandin-resistant strains. We report pts with CMC enrolled in an ongoing Ph 3 study of IBX (NCT03059992) for treatment of pts with disease refractory to/intolerant of SOC antifungal therapy.

Methods: Pts were treated with OL IBX. An independent Data Review Committee (DRC) provided response assessment for pts at end of treatment (EoT: 90 d postdose), and 3 pts who continued therapy beyond EoT (10/2021).

Results: There were 30 pts with CMC (mean age of 55 yr), 19 (63%) had defined innate immune dysfunction, 8 (27%) had secondary immune deficiency and 3 undocumented. At EoT, 9/19 pts w/innate immune dysfunction had complete/partial response, 7/19 had stable response, 2 w/disease progression (1 death due to underlying disease). Mean duration of IBX = 67.1 d. As of data cut-off, 1 pt received treatment for >1 yr, 1 pt >2 yr, and 1 pt >3 yr. No safety issues have been identified with prolonged treatment.

Conclusions: Oral IBX offers a promising, safe and well-tolerated alternative treatment for these patients with limited treatment options.

P100

Clinical evaluation of milk and egg-ladder in children with milk and egg allergy

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Background: Milk and egg are the most frequent food allergies (FA) in the first year of live. As most of the patients already tolerate baked milk and egg at this age, stepwise introduction with progressively less cooked egg and milk, the so called “milk and egg ladder” has increasingly been used as a treatment for these FA. As the regular exposure to the foods, to which the child potentially reacts, is taken place at home, some parents find it more challenging than others to proceed with this therapy option. At the moment, we provide appointments every 3 to 6 months, with the possibility to contact us whenever needed.

Aim of the study: Investigate how to improve our daily practice to offer best support to families.

Methods: Through an anonymous and retrospective questionnaire, we asked parents of children with milk or egg allergy about difficulties concerning the therapy option.

Results: In the first 20/52 completed surveys, we can observe that about 50% of the patients experienced a low grade reaction (mainly perioral urticaria) following to a change in level, treated with antihistamines. 13/20 completed all stages of the milk and egg ladder successfully. The offered support was sufficient for the families.

Conclusion: We confirm, that the milk and egg ladder, is a safe and effective treatment option for milk and egg allergies. The therapy can be good incorporated into everyday life and the offered support with regular appointments and email or phone contact with nutritionist and allergist seemed to be sufficient for the families.

P101

DRESS folllowing vaccination for COVID-19: a case compatible with the concept of molecular mimicry

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Introduction: Few reports of severe cutaneous adverse reactions following COVID-19 vaccines exist and causes remain to be elucidated. We describe a case of DRESS syndrome (drug rash with eosinophilia and systemic symptoms).

Case report: A 52-year-old woman presented with a generalized rash occuring 1 day after vaccination with the Moderna vaccine. The patient met clinical criteria defining a probable DRESS syndrome. Investigations included a lymphocyte transformation test to the excipient trometamol showing increased proliferation. A consecutive vaccination with Janssen® COVID-19 vaccine led to a recurring rash of lesser severity.

Discussion: This case shows the development of DRESS following administration of the Moderna mRNA vaccine. The course of symptoms with recurrence of a rash after the consecutive vaccination with

the vector based Janssen® vaccine suggests a common elicitor of the adverse reaction. COVID-19 vaccine induced adverse events may be caused by molecular mimicry with human proteins due to structural similarities with SARS-CoV-2 sequences.

Conclusions: Careful allergological work-up reveals some causes of hypersensitivity to COVID-19 vaccines, with sensitization to trometamol possibly playing a role in this case. The spike glycoprotein is suspected as a main driver of adverse skin reactions. Bringing light to the underlying mechanisms of cutaneous reactions to SARS-CoV-2 vaccine is necessary for prevention and treatment.

P102

On the role of allergen-specific IgG4 for blocking basophil activation

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IgG4 has multiple implication in health and clinical applications. Most prominently in allergen-specific immunotherapy (AIT) and as therapeutic antibodies. During AIT IgG4 is the prominent subclass being produced as a result of the treatment, while in therapeutic applications IgG4 is used based on its anti-inflammatory properties. Interestingly, IgG4 undergoes arm exchange by exchanging a heavy-light chain pair two distinct IgG4 molecules, creating bispecific IgG4. This process is of interest because it has been observed in vivo in humans. However, it is still not clear whether IgG4 prevents allergen-induced inflammation more efficiently than other IgG subclasses. Therefore, our project aimed to compare allergen-specific IgG1 and IgG4 antibodies in their capacity to inhibit type I allergic reactions. In a first set of experiments using allergen specific monoclonal IgG1 and IgG4 we found that both antibody subclasses bind with a similar affinity to FcgRIIb and have the same capacity to block human basophil activation; both by neutralizing the allergen as well as by engaging FcgRIIb. This shows that the IgG subclass plays a limited role in AIT. Next, as natural IgG4 antibodies are mostly bispecific we produced a bispecific recombinant IgG4 antibody containing two antigen binding sites specific for two different allergens. Analysis of purified bispecific IgG4 in regard to its binding affinity to antigen, IgG receptors and its capacity to block basophil activation will allow to determine its anti-inflammatory properties compared to its monospecific IgG4 counterparts.

P103

A coronin 1-dependent kin-to-kin density-sensing pathway defines T cell population size

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The maintenance of appropriate cell population size is fundamental to the proper functioning of multicellular organisms, yet the underlying mechanisms remain largely undefined. For T cells, the factors required for their sustained survival in the peripheral lymphoid tissues are well described, but it is unclear how the homeostatic population size is defined. We have used a combination of techniques including cell biology, biochemistry, molecular biology, and different model systems including humans to study the regulation of cell population size. We found and described a cell-intrinsic kin-to-kin density-sensing pathway that allows T cells to define their appropriate population size. Cell density-dependent expression of coronin 1 protein coordinated pro-survival signaling with inhibition of cell death until the cell population reached threshold densities. At or above threshold densities, coronin 1 expression leveled off allowing for the initiation of apoptosis through kin-to-kin adhesin-mediated signaling to return the cell population to homeostatic cell size. Mice and humans that lack coronin 1 have up to 90% reduction of mature T cells in circulation, with severe defects on the regulation of immunity. Our data suggest the existence of a coronin 1-regulated homeostatic mechanism by which T cells are informed of and coordinate their population size.

P104

Online management of allergic patients for COVID-19 vaccination: a real-world single center experience

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Background: In the canton de Vaud, 604'633 individuals received at least one dose of COVID-19 vaccine. An online evaluation form was built to identify patients at increased risk of anaphylaxis and facilitate the in-center triage.

Aim: To evaluate the outcomes of the vaccination, allergic reactions and satisfaction level of this online screening method.

Methods: Individuals with documented allergy to any vaccine components and/or who suffer from severe allergic reactions to infused or injectable drugs were asked to fill an online form to define their eligibility for mRNA vaccines by an allergist. Several months after this assessment, a survey was sent back to get feedback on the outcomes of the vaccination status.

Results: 3519 (0.58%) individuals underwent online risk assessment for mRNA vaccines. Of those, 1658 (47%) completed the survey. 80.4% had received two doses. Frequent adverse events included fever (24%), headache (27%), fatigue (39%) and muscular/articular pain (28%). Of the 420 (27%) who reported to be asthmatic, 12.8% complained worsening of asthma control after vaccination. Severe allergic reactions were reported in 24 (1.5%) cases and, after online review, considered as possible in 10 cases (0.6%). The median satisfaction and reassurance of the online form were 91/100 and 98/100, respectively. Satisfaction was significantly influenced by age and the number of vaccines received (0-vs-1-vs-2).

Conclusions: Providing an online assessment for vaccine eligibility from an allergist reassured the allergic population and may represent a valuable tool to increase vaccine adherence.

P105

New onset of chronic spontaneous urticaria ten days after the mRNA vaccine booster of Moderna

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Background: The COVID-19 vaccines from Moderna and Pfizer represent 62% and 37% of the doses administered in Switzerland, respectively. By 28 June 2022, 1,228 reports of urticaria were submitted to Swissmedic, mainly after the first booster (= 3rd dose) after primary vaccination.

Aims: To define the patient's characteristics, timing, and mechanisms driving the onset of chronic spontaneous urticaria (CSU) after mRNA vaccines.

Methods: Based on a collaborative effort with local practitioners, we identified 88 patients suffering from CSU. An online survey was submitted for further characterization of CSU. Basophil activation tests (BAT) with the mRNA vaccines were performed in 27 patients.

Results: Seventy-one patients (80%) completed the survey. 75% were women. The median age was 41 (IQR:35-48). In 92% of the cases, urticaria started after the 3rd dose. Median days between vaccination and onset of CSU were 10 (IQR: 8-12). In 93% of the cases, patients received the Moderna vaccine. At the time of the survey, CSU was active in 86% of the cases representing a median duration of 115 days (IQR: 101-140). Inductile urticaria was reported in 38 patients (54%), mainly as symptomatic dermographism. BAT were not interpretable in 26% (n = 7), yet in 50% (n = 10) of the cases, they were positive for the mRNA vaccines.

Conclusion: CSU was mainly reported after the booster dose of Moderna in adults at their 40s. It was associated with a high rate of sensitization against mRNA vaccines. Urgent studies are needed to

establish whether a definitive link exists between CSU and booster doses with mRNA vaccines.

P106

SARS-CoV-2 Vaccinations do not confer protection against Omicron variants: COVID naïve, naturally immunized and vaccinated patients have the same symptoms

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Background: COV_{19}-ID score questionnaire and its lab model are useful for early triage of COVID-19 patients, alleviating the burden on laboratories, emergency rooms and hospital wards. End of December, Omicron variants appears, Delta strains disappears. Other viral diseases than COVID-19 are back, needing to be distinguished. **Aim:** Adapting previous screening questionnaires.

Methods: Analysis of clinical data from informed and consenting patients with Omicron COVID between January 1st and June 30th. Information was collected from patients from the COVID centre [CoC] and the Clinical Immunology Unit [CIU] of Hôpital de la Tour.

Results: Data analysed: 7752 CoC patients (M 46%,F 54%,Vac 70%, noVac 30%), 168 CIU patients (M 29%,F 71%,Vac 61%,noVac 39%). All RT-PCR+ were analysed for early (CoC & CIU) and persistent symptoms (CIU). Most common and relevant symptoms: cough, fever, rhinorrhoea, headache, sore throat, history of contact, muscular stiffness, fatigue. No clinical or statistical difference between Vac and noVac patients. Persistent fatigue, lasting sore throat, susceptibility to infections (sinusitis, bronchitis) were reported for ≥ 4 months in >45% of CIU. Severity of symptoms: much less severe than with β,g,α or d variants.

Conclusion: Reported symptoms are statistically different from those of the 2 previous years of pandemic. Screening questionnaires and scores remain useful for the early triage, in discriminating between SAR-CoV-2 and other viral infections, follow-up of Long COVID syndrome, but need to be adapted with each variant of consequence of SARS-CoV-2.

P107

Longitudinal study of clinical and immune responses post Omicron infection in non-vaccinated and vaccinated subjects with or without previous COVID

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Background: Since end Dec. 2021, the Omicron SARS-CoV-2 strains have appeared while previous β,g,α or d strains have disappeared.

Methods: Analysis of clinical, humoral, cellular and inflammation responses in known patients from the Clinical Immunology Unit [CIU] after Omicron COVID. Recruitment January 1st to June 30th, 2022. Comparison with data of 54 CIU COVID patients from the first wave [1stW]. Measured parameters: β2microglobulin [β2m], C3, C4, ferritin, ECP, anti Spike1 [S1] for Wuhan and Omicron B1.159, ab anti NCP (nucleocapsids) and neutralizing antibodies [NeuAb], Ab phenotyping, leucocyte repartition, lymphocyte phenotyping. Patients: 118 Omicron infected [OmiP]: M 31%, F 69% (Vac 64%, noVac 36%): 24 previously "Naïve COVID" [NaCOV], 18 noVac with a previous β,g,α or d COVID, 64 Vac with no previous COVID and 12 Vac with a previous COVID.

Results: No difference between OmiP and 1stW in the kinetics of response to S1 (Omicron or WT) in the first 6 months. It peaks between 45 to 60 d. Anti-NCP ab peaks at 30 to 45 d and is still present ≥ 5 months. Prior infection and/or vaccination is associated with a 2-3-fold increase of previously detected anti-S1 Wuhan and anti- S1 Omicron. NaCOV develop ab to S1 Wuhan but in much lesser amounts than 1stW. Among OmiP no increased counts of eosinophils and NK as observed in 1stW, neither any increase in β2m and CRP. The majority of OmiP have elevated serum ECP and increased polyclonal ab production for ≥ 4 months.

Conclusions: Omicron induces a different immune response than previous strains of SARS-CoV-2.

P108

Hepatitis E virus infection in cancer patients

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Background: Hepatitis E virus (HEV) infection can lead to chronic hepatitis and liver failure, but the burden of HEV in cancer patients is unknown.

Aims: We studied the characteristics of HEV infection in patients at a cancer center in the United States.

Methods: Retrospective study of adult cancer patients with HEV diagnosed at MD Anderson Cancer Center (09/01/2011-09/01/2021). Acute HEV infection was defined as an acute increase of liver enzymes with HEV RNA or HEV IgM detection. Chronic HEV infection was defined as detectable HEV RNA ≥ 3 months.

Results: A total of 405 patients were tested for HEV, and 63 (16%) had detectable HEV IgG. Of them, 46 (73%) were screened for HEV because of pre-existing liver conditions, and 22 (35%) had hematological malignancies. Only 2 patients had detectable HEV RNA, both with hematological malignancies. None of them developed HEV-related liver failure. The first patient had myelodysplastic syndrome post allogeneic stem cell transplant. He received prednisone for graft versus host disease. After tapering steroids, viral clearance occurred within 2 months. The second patient had diffuse large B-cell lymphoma treated with anti-CD19 chimeric antigen receptor (CAR) T-cell therapy. She was not receiving immunosuppressants. Ribavirin was started for 12 weeks but she failed therapy, now on an extended course of ribavirin for 24 weeks.

Conclusions: This is the first report of chronic HEV infection post CAR T-cell therapy. Patients with hematologic malignancies may be at risk of HEV refractory to treatment.

P109

Immunization protocol with adjuvant ArtinM favors the control of *Cryptococcus gattii* infection in C57BL/6 mice

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The incidence of invasive fungal infections (IFI) has increased and the development of new antifungal drugs with low adverse side effects have been inefficient, then other therapeutic strategies against IFI are in progress. Our group previously observed that the administration of a dectin-1 agonist associated with immunization with heat-killed *C. gattii* was able to promote a reduction in the fungal burden of C57BL/6 mice. The immunomodulation of host immune is a promising way to treat IFI, and the immunomodulatory activity of ArtinM was efficient to control of fungal infections caused by *P. brasiliensis* and *C. albicans*. Thus, the effect of adjuvant ArtinM as an TLR2 agonist was evaluated in the vaccination against *C. gattii* infection. For this, C57BL/6 mice were divided into four groups: (i) untreated group; (ii) immunized group; (iii) TLR2 agonist group; (iv) TLR2 agonist plus *C. gattii* group. The vaccination cited above was performed on days 3, 17, and 31 with the administration of 2×10^7 yeast/mouse of H.K-*C. gattii* via i.n. Mice of the TLR2 group showed reduced IL-10 levels compared to immunized group, and reduced expression of IL-23 compared to the untreated group. Furthermore, TLR2 agonist group showed a lower frequency of positive mice for mucicarmine staining, and a higher percentage of area with inflammatory infiltrate compared to the immunized group, with a consequent reduction in CFU. These data evidenced that administration of ArtinM TLR2 agonist favored the control of *C. gattii* burden in the lung of C57BL/6 mice.

P111

Improved outcomes over time and higher mortality in CMV seropositive allogeneic HCT patients with COVID-19: a study from the EBMT registry

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Background: COVID-19 has been associated with high mortality in allogeneic hematopoietic stem cell transplant (allo-HCT) recipients.

Aim: To study outcome over time and identify risk factors for mortality in patients reported to the EBMT registry.

Methods: 776 allo-HCT patients reported during the first 21 months of the pandemic up until Nov. 2021 were included. Cox regression models were produced to assess risk factors for mortality.

Results: The median age was 49.4 years (min-max; 1.0 – 80.7). The median time from HCT to COVID-19 diagnosis was 14.1 (0.0–292.7) months during the first period (February 28 – July 31, 2020), 24.4 (0.1–287.6) months during the 2nd (August 1, 2020 – January 31, 2021), and 24.8 (0.1–324.5) months during the 3rd (February 1 – November 30, 2021). 110/776 (14.2%) patients died a median of 21.5 days after diagnosis of SARS-CoV-2 infection. Children had a significantly lower mortality than adults. In multivariate analysis, increasing age (HR 1.27 (95% CI 1.11-1.44; p = .0004), worse performance status (HR 1.48 (1.32-1.65; p <.0001), contracting COVID-19 within the first 30 days after HCT (HR 4.69 (2.44-9.02); p <.0001), ongoing immunosuppression (HR 2.05 (1.20-3.50); p = .009), and recipient CMV seropositivity (HR 2.38 (1.25-4.52); p = .008) had negative impact on overall survival while patients contracting COVID-19 in the 2nd or 3rd period had higher overall survival (p = .0003).

Conclusion: Although the outcome of COVID-19 has improved, patients having risk factors still showed high mortality and preventive measures have to be taken.

P112

Carbohydrate-conjugated house dust mite allergen, group 2 *Dermatophagoides pteronyssinus*, inhibits T helper 2 responses in PBMCs in vitro

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Group 2 *Dermatophagoides pteronyssinus (*Der p 2) is a major allergen group produced by the European house dust mite, a causative agent of allergic asthma. Because available allergen immunotherapy (AIT) regimens are lengthy and still carry a high risk of side effects, new, safer, and shorter AIT options are needed. One promising novel AIT strategy includes the conjugation of allergens to carbohydrate residues to target inhibitory immune cell receptors such as Sialic acid-binding Immunoglobulin-type lectins (Siglecs), to restore immune dysregulation. It has been reported that ligands of Siglecs, sialic acids, conjugated to peptides of pollen allergen, *Phleum pratense* 5a, induce a tolerogenic profile in dendritic cells that mediate the induction of suppressive T cells and alleviate allergic asthma in mice. In this study, we conjugate a Siglec ligand (α2,3 sialic acids) to Der p 2 and evaluate their effects on human PBMCs *in vitro*. We stimulate PBMCs with anti-CD3 and CD28 antibodies and culture them for 6 days in the presence of Der p 2. Supernatant is used to measure cytokine levels by ELISA and the cells are stained to measure expression of T cell activation markers. We show that, sialic acid conjugated-Der p 2 inhibits T cell activation, inhibits the secretion of Th2 cytokines such as IL-5, and induces the secretion of suppressive cytokines such as IL-10. In conclusion, sialic acids conjugated to Der p 2 induces a tolerogenic profile in PBMCs and could therefore be exploited for improvement of AIT.

P113

Tofacitinib use in the management of refractory systemic sarcoidosis: second case reported in the literature

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Background: Sarcoidosis is a polymorphic systemic disease characterized by inflammatory granulomas affecting the lungs and other organs. Overall mortality is high (6.7%), especially in refractory case to available therapies. Tofacitinib is a novel tyrosine kinase inhibitor, used in rheumatoid arthritis, psoriatic arthritis and ulcerative colitis. One available case report describes the benefit of tofacitinib in a case of corticosteroid-refractory systemic sarcoidosis.

Aim(s), purpose or hypothesis: We present the case of a 32 years old woman known for a chromosome 18 microdeletion syndrome and a severe systemic sarcoidosis with lung, heart and brain involvement. Methotrexate and azathioprine could not be used because of strong gastrointestinal side-effects. Infliximab was suspended after anaphylactoid reaction to the treatment and the positivity of neutralizing anti-drug antibodies. The disease was refractory to prednisone, mycophenolate mofetil and cyclophophamide.

Methods: We introduced tofacitinib 5 mg 2x/day and we followed clinical, biological and radiological evolution over time.

Results: Tofacitinib treatment benefited to the patient with a dramatic improvement of the disease activity at clinical, biological and radiological levels. No complication was documented 8 months after the beginning of this new treatment.

Conclusions: This case illustrates the promise of JAK inhibitors as a strategy to treat refractory systemic sarcoidosis, although further studies are needed to assess their efficiency and security in this disease.

P114

Duplex nucleic acid testing for dual detection of wildtype and mutants defining SARS-CoV-2 variants of concern

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Background: Accurate detection of SARS-CoV-2 (SCoV2) variants of concern (VOCs) is pivotal as they affect transmission, monoclonal antibody therapy and escape from natural and vaccine-induced immunity.

Aim: We developed nucleic acid testing (NAT) for dual detection of SCoV2 wildtype and mutant sequences of the spike gene (Del69/70, L452R, E484A, E484K, N501Y) defining specific VOCs (Basel-SCoV2-WT/MUT).

Methods: The retrospective study cohort (n = 77) consisted of SCoV2 wildtype and Alpha, Beta, Gamma, Delta and Omicron VOCs as defined by whole genome sequencing (WGS). The prospective study cohort (N = 249) consisted of locally circulating Omicron BA.1, BA.2 and BA.5 variants. Both cohorts were also analyzed using a commercially available test (Roche cobas®-SCoV2-variant assay).

Results: Basel-SCoV2-WT/MUT accurately identified all VOCs in the retrospective study cohort. SCoV2 RNA copy numbers <1'000 copies/mL decreased the efficacy of the Basel-SCoV2-WT/MUT NAT. At these low SCoV2 RNA levels, the cobas®-SCoV2-variant assay showed partial or full drop-outs leading to false-negative results. In the prospective study cohort, Basel-SCoV2-WT/MUT accurately identified Omicron BA.1, BA.2 and BA.5 variants by detecting Del69/70 mutant and wildtype sequences, including four patients with WGS confirmed co-infection undetected by the cobas®-SCoV2-variant assay.

Conclusion: In conclusion, Basel-SCoV2-WT/MUT is accurate and allows rapid and low-cost detection and differentiation of SCoV2 VOCs. Importantly, the assay can be readily adapted to new spike mutations as new SCoV2 variants emerge.

P115

Impact of SARS-CoV-2 Omicron on rapid antigen testing developed for early pandemic SARS-CoV-2 variants

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Background: Rapid antigen tests (RATs) are widely used for point-of-care or self-testing to identify SARS-CoV-2 (SCoV2)-positive cases.

Aim: To assess the performance of RATs with currently circulating Omicron variants that may impair detection.

Methods: We prospectively evaluated the Roche-SARS-CoV-2-Antigen and Acon-FlowFlex-SARS-CoV-2-Antigen in 150 consecutively collected nasopharyngeal patient swabs (50 SCoV2 RNA undetectable; 100 SCoV2 Omicron BA.1). Omicron BA.1 results were compared to 92 Ct-matched early pandemic SCoV2 variants (B.1.160 and B.1.177), to 100 Omicron BA.2 positive and to 100 Omicron BA.5 positive samples.

Results: For Omicron BA.1, Roche-SARS-CoV-2-Antigen detected 87% of samples having Ct-values <29 reflecting 3.6% lower rates compared to B.1.160 and B.1.177. Acon-FlowFlex-SARS-CoV-2-Antigen was less affected and detected 90% of Omicron BA.1 with Ct-values <29. Omicron BA.2 and BA.5 detection rates were significantly reduced by 20% and 10%, respectively, for the Roche-SARS-CoV-2-Antigen in samples with Ct-values <29, but remained similar for Acon-FlowFlex-SARS-CoV-2-Antigen. RATs need to be continuously evaluated as new SCoV2-variants emerge.

Conclusion: This study provides evidence that variation within the nucleocapsid protein as seen in recently emerged and now globally spreading Omicron BA.2 and Omicron BA.5 variants significantly impairs detection rates of widely used antigen tests. Consequently, antigen tests need to be re-evaluated when new pandemic SCoV2 variants emerge and start to predominate globally.

P116

Systematic review of safety and efficacy of IL-1-targeted biologics in treating immune-mediated disorders

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Background: The cytokine interleukin (IL)-1 plays a pivotal role in immune-mediated disorders, particularly in autoinflammatory diseases. Targeting this cytokine proved to be efficacious in treating numerous IL-1-mediated pathologies. Currently, five IL-1 blockers, namely anakinra, canakinumab, rilonacept, gevokizumab and bermekimab, are approved or expected to receive approval. However, there is no systematic review on the safety and efficacy of these biologics in treating immune-mediated diseases.

Aim: To evaluate safety and efficacy of these five IL-1 blockers in treating immune-mediated disorders.

Methods: We searched the PubMed database, according to the PRISMA checklist. Our literature search identified 7363 articles. After screening, 75 articles were included in a narrative synthesis.

Results: The analyzed IL-1 blockers were efficacious and safe in treating cryopyrin-associated periodic syndromes, familial Mediterranean fever, gout, hidradenitis suppurativa, hyper-IgD syndrome, macrophage activation syndrome, recurrent pericarditis, rheumatoid arthritis, Schnitzler's syndrome, systemic juvenile idiopathic arthritis, TNF receptor-associated periodic syndrome and urticarial vasculitis. Conversely, they showed mixed results or failed to show efficacy in adult-onset Still's disease, Behcet's disease, graft-versus-host disease, psoriasis arthritis, pyoderma gangrenosum, Sjögren's syndrome and type 1 diabetes mellitus.

Conclusions: This systematic review of IL-1-targeting biologics summarizes the current state of research, safety, and clinical efficacy of five IL-1 blockers.

P117

COVID-19 outcomes in solid organ transplant patients given tixagevimab-cilgavimab prophylaxis and/or bebtelovimab treatment in a nurse-led program

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Background: Incidence of COVID-19 Omicron infection in SOTR is high, but there are few data on interventions after BA.1. Tixagevimab-cilgavimab (TC) was available for pre-exposure prophylaxis (ppx) as of 1/2022: and bebtelovimab (BEB) as treatment in 4/2022 with the rise of BA.2.

Aims: We aimed to describe Omicron outcomes in SOTR at a single US center through 7/9/22, focusing on TC (ppx) and BEB (treatment).

Methods: Candidates for TC were identified by electronic medical record (EMR), referrals, and RN outreach. EMR eports of positive SARS-COV-2 tests in SOTR were generated daily. NPs and RNs helped arrange BEB for those who met criteria.

Results: 213 SOTR received TC (197 got 300/300mg), and 22(10.3%) developed COVID-19; 3 were hospitalized, 1 required mechanical ventilation (MV), 2 died (one with BA-1). 4 (18.2%) cases were <14 days after TC. 7 (3.3%) patients had cardiac events, with median time of 13 weeks post TC.

212 SOTR were diagnosed with COVID-19 from 4/4/22-7/9/22 (127 kidney, 30 liver, 18 lung, 27 heart, 10 dual). 145 (68.4%) were treated with BEB; of those, 18 (12.4%) were hospitalized, 1 required MV, and 1 (0.7%) died.

Conclusions: Despite large numbers of Omicron cases, almost 90% of SOTR who received TC did not contract COVID-19; of the 10.3% who did, most had mild disease and 2 died. 7 cardiac events were reported after TC, but relationship to TC is unclear. SOTR with COVID-19 who received BEB had low rates of hospitalization and 1 death. These favorable outcomes underscore the value of an RN-led program for rapid referral for monoclonal antibody ppx or treatment.

P118

SARS-CoV2 infection in non-VIH immunocompromised patients admitted to a general hospital during the COVID-19 pandemic

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Introduction: Covid-19 is associated with high mortality (M) in immunocompromised hosts (ICH) and can vary in different types of ICH and immunosuppression (IS).

Objectives: 1. Describe and compare clinical, epidemiologic and evolutionary (CEE) of Covid-19 hospitalized ICH. **2. C**ompare ICH vs. non-ICH (NonICH) M; analyze independent risk factors (IRFs) of immunocompromise (IC) associated M.

Methods: prospective and observational. Adult ICH -Onco-hematological (OH), solid tumors (ST), solid organ transplants (SOT) and autoimmune diseases (AD)- hospitalized with Covid19 (March 2020/May 2022). Compared CEE between them. Compared M between ICH and contemporaries 1168 NonICH. Clinical presentation (CP): NIH scale. Active treatment (AT): IS or chemotherapy. Incomplete vaccination (VI)

Statistics: ANOVA and Tukey's post hoc tests for groups comparison. Survival analysis Kaplan Meier curves. Multivariate Analysis (MA) to analyze RF associated M.

Results: ICH: 217; OH: 61, ST: 88, SOT: 26, AD: 42. No statistically significant difference (SSD) in CEE, and M between ICH groups. M: SSD in ICH: (37/217: 17%) vs NonICH (156/ 1358: 11.5%) p: 0.02. Severe Community-acquired pneumonia (SCAP) in ICH: 37/92 (40%) vs NonICH: 83/522 (16%) p: 0.0001. MA adjusted for age and

sex: SCAP was the only IRF for M (OR: 4; 95% CI: 1.9546-9.1758). SOT, ST, AT and VI had higher death risk without SSD.

Conclusions: SCAP was IRF for mortality. Immunocompromise alone and with SCAP had higher overall mortality. This highlights the need to apply early preventive and therapeutic measures in ICHs.

P119

SARS-CoV2 infection in oncohematological patients admitted to a general hospital

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Introduction: Oncohematological patients (OHP) with Covid19 (C19) can develop serious and lethal complications. It depends on underlying disease, chemotherapy (ChT) and immunosuppressor (IS) prescribed.

Objectives: compare mortality (M) in OHP vs. hospitalized normal hosts (NH); analyze independent risk factors (IRFs) of M.

Methods: 3/2020-5/2022; population: OHP with C19. Prospective, observational data collection. Clinical presentation: NIH scale; Active treatment (AT): IS or ChT; Complete C19 vaccination (CV). Statistics: ANOVA and Tukey's post hoc tests for comparison of groups. Multivariate test to analyze IRFs associated with M.

Results: OHP: 62; MM: 19.3%; LLC: 21%; Lymphomas: 24.2%; ALL: 11.3%; AML: 9.7%; MDS: 14.5%. Age: 68 (17-88); Male sex: 77.4%; moderate CAP: 72.6%; Severe CAP: 27.4%; CV: 22.6%; neutropenia (NP): 22.6%; AT: 61.3%. MM was associated with higher M. OD: 5.3 (95% CI 1.1742 -24.1685). OH had higher M statistically significant difference (SSD)- vs. ICP (12/62): 19% vs. (118/1168): 10%; p: 0.02. Multivariate analysis adjusted for age and sex: MM (OR: 5.32, 95% CI: 1.1742–24.1685) and Severe CAP (OD: 11.23, 95% CI: 2.0636 - 61.1310) were IRFs associated with M. AT (OR: 3.2) and NP (OR: 4.18) had higher risk of M with nonSSD; CV (OR: 0.66 95% CI 0.1110–4.0235) had lower risk without SSD. **Conclusions:** MM and severe CAP were IRFs for M. CAP was associated with higher M in OHP than NH. CV could be a protective factor without SSD. The high M documented in OHP with C19 justifies implementation of early preventive measures and treatment in this population.

P120

Factors impacting the medication “adherence landscape" for transplant patients

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Background: Medication non-adherence contributes to post-transplant graft rejection and failure; however, limited knowledge about the reasons for non-adherence hinders the development of interventions to improve adherence. We conducted focus groups with solid organ transplant recipients regarding overlooked challenges in the process of transplant medication self-management and examined their adherence strategies and perceptions towards the post-transplant medication regimen.

Aims: Gain a better understanding of the modifiable and non-modifiable factors affecting patient immunosuppression adherence post-transplantation.

Methods: We conducted four focus groups with n = 31 total adult transplant recipients. Participants had received kidney, liver, and/or pancreas transplants at Johns Hopkins Hospital between 2014-2019. Focus groups were audio-recorded and transcribed. Transcripts were analyzed inductively, using the constant comparative method.

Results: Responses generally fell into two major categories: (1) barriers to adherence and (2) “adherence landscape”. We define the former as factors directly labeled as barriers to adherence by participants and the latter as factors that heavily influence the post-transplant medication self-management process.

Conclusions: We propose a shift in the way healthcare providers and researchers, address the question of medication non-adherence. Rather than asking why patients are non-adherent, we suggest that constructing and understanding patients’ “adherence landscape” will provide an optimal way to align the goals of patients and providers and boost health outcomes.

P121

A novel VLP-based glycoengineered vaccine against Actinobacillus pleuropneumoniae

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Livestock plays a fundamental role in the food security worldwide. The infectious diseases diagnosed on animal farms are a great threat to animal welfare as well as to economic returns. Lack of available vaccination against many pathogenic bacterial species leads to overuse of antibiotics and, in consequence, to increase of antimicrobial resistance in the environment. Therefore, development of effective anti-bacterial vaccines, with low cost and simple manufacturing processes is a highly unmet medical need.

Actinobacillus pleuropneumoniae (APP) is a pig pathogen causing contagious porcine respiratory disease. The structure and biosynthesis of glycoprotein adhesins from this species lay the basis for the generation of vaccine targeting these pathogens. Here, we developed a novel vaccine candidate against APP based on virus-like particle (VLP) technology platform. Cucumber Mosaic Virus-derived monomers ($CuMV_{TT}$) were genetically fused with sequences possessing N-glycosylation sites and co-expressed in *E. coli* with APP-derived N-glycosylation system, consisting of two enzymes: ApNGT and an α1,6GlcT, which allow for efficient glycosylation of the VLPs while preserving their undisturbed assembly. MS analysis confirmed the dextran-like glycosylation pattern of VLP subunits with up to 10 glucose residues. Immunizations of mice with these VLPs resulted in a significant anti-dextran IgG response, providing a strong evidence for vaccine immunogenicity. Current *in vivo* experiments are focused on the efficacy of the vaccine-induced IgG in inhibition of APP adhesion to their target cells.

P122

Chronic spontaneous urticaria after COVID-19 mRNA vaccination

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Introduction: Skin manifestations after COVID19 vaccination are usually transient and self-limiting. In daily clinical practice, we observe an increasing number of chronic spontaneous urticaria (CSU) cases after mRNA-COVID19 vaccination (mRNA Co19Vac).

Aims: To present the clinical features of patients with CSU after mRNA Co19Vac.

Methods: This is a cross-sectional study in which all patients with a new onset of CSU within 2-3 weeks following mRNA Co19Vac were analysed. All data were collected from medical records.

Results: We included 26 CSU patients with a mean age of 40 years (SD ±12.1), 16 were female (62%). In all but 3 cases, CSU was induced by booster vaccination. In 2 cases, CSU occurred after the 2nd vaccination and in 1 case after the 1st vaccination. All of our patients received mRNA-1273 vaccine. The mean latency from vaccination to disease onset was 11 days (SD±3.9). No major laboratory abnormalities occurred in any of the cases. One patient had an elevated basal serum tryptase (bST) level (17.5 µg/l). The mean bST of the remaining patients was 3.8 µg/l (SD±1.1). In 4 out of 23 patients (17%) low total IgE levels (<10 kUL) were observed. In 6 patients (26%) the values were higher than 100 kUL (SD±443).

The clinical course of urticaria was favorable in most cases. Treatment with omalizumab was initiated in 1 patient with antihistamine-resistant CSU.

Conclusion: Our study suggests that mRNA Co19Vac with mRNA-1273 may act as a CSU trigger in patients without a history of urticaria. In rare severe forms, patients could potentially benefit from treatment with omalizumab

P123

Evaluation of extracellular vesicles as noninvasive early predictive markers for severe COVID-19

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Background: There is an urgent need to identify novel biomarkers for early detection of severe cases of COVID-19. Extracellular Vesicles (EVs) contain cargoes derived from the cell of origin that include proteins, lipids, and nucleic acids and have been used as biomarkers in other diseases.

Aim: To identify EVs-derived biomarkers in broncho-alveolar lavages (BAL) and plasma for the early detection of severe COVID-19.

Methods: We included patients hospitalized without and with severe COVID-19 and non-hospitalized mild cases. EVs were isolated from BAL and plasma, and characterized by western blot, electron microscopy and mass spectrometry-based proteomics. EVs derived proteins in both BAL and plasma from severe cases but not from mild or controls will be selected to generate a mathematical model to distinguish severe from mild and non-COVID-19. An independent validation cohort will be used to evaluate sensitivity and specificity.

Results: We isolated EVs from BAL and plasma of non-COVID-19 patients and optimized the protocol for mass spectrometry. The EVs isolated were expressing the common EVs markers such as CD63, stomatin and TSG101 and electron microscopy confirmed the enrichment of EVs after isolation. Proteomic analysis showed a great overlap in the EVs proteins detected between different patients. We found 80% of the proteins were EVs derived confirming the EVs isolation protocol.

Conclusions: Isolated EVs from plasma and BAL showed characteristic markers, microscopy patterns and proteomic analysis compatible with EV origin. We are currently isolating EVs from COVID-19 patients and would identified proteins that allow us to predict COVID-19 severity.

P124

Perioperative anaphylaxis: consider more than one drug?

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Background: Allergy workup of perioperative anaphylaxis requires a large set of skin and often *in vitro* tests. Generally one single culprit drug is identified, but co-sensitizations can also occur.

Aim: To describe a case of perioperative anaphylaxis with multiple culprit drugs identified.

Methods: case report

Results: A 69-years old woman was hospitalized for an *in situ* breast ductal carcinoma surgery. She was known for a hypersensitivity reaction to penicillin (1995) and a possible anaphylaxis after iodinated contrast media during childhood. She has had several surgical interventions in the past that were uneventful. During the described intervention, she experienced two anaphylactic events. The first one occurred two hours after anesthesia induction and consisted of a generalized urticaria which responded to corticosteroids and antihistamines. Four hours later, she presented an anaphylactic shock, successfully treated with intravenous hydration and repeated anaphylaxis treatment. Tryptase leves were always in the normal range with no significant variations, there were no other signs for cutaneous or systemic mastocytosis. The allergologic workup (skin and *in vitro* BAT tests) revealed a sensitization to Patente Blue dye, ketamine, rocuronium and atracurium as well as betalactam antibiotics. During the skin testing she experienced a systemic reaction compatible with anaphylaxis, again without tryptase elevation.

Conclusions: This case illustrates the possibility, even if rare, of multiple synchronous sensitizations being involved in one single reaction. It further illustrates that anaphylaxis can occur without significant peak tryptase elevation.

P125

The lack of mortality benefit from ribavirin in patients with stem cell transplantation and hematologic malignancy with respiratory viral infections

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Background: Evidence to guide treatment recommendations for respiratory viral infections (RVIs) in patients with hematologic malignancies (HMs) and hematopoietic stem cell transplant recipients (HSCTs) remains scarce and conflicting.

Aim: To describe clinical outcomes of 3 different RVIs including respiratory syncytial virus (RSV), parainfluenza virus (PIV), and human metapneumovirus (HMPV), and evaluate mortality benefit of ribavirin for these 3 RVIs.

Method: Random-effects models for meta-analysis and descriptive statistics were used.

Results: A total of 29 studies were included for the systematic review and 12 studies in meta-analysis, representing 1,916 HSCTs/HMs with 3 RVIs. The pooled rates (range) of mortality, disease progression from upper to lower respiratory tract infections, and intensive care unit admission were 17.7% (0-50), 21% (0-100) and 10.1% (0-27.3) for RSV; 14% (0-62.5), 26.1% (11-81) and 3.23% (0-4.2) for PIV; 11% (0-33), 31.3% (18-40) and 13.3% (1 study) for HMPV, respectively. Ribavirin use was not associated with reduced mortality with the pooled odds ratio [95% confidence interval (CI)] of 1.2 [0.5, 2.6] and 0.7 [0.3, 1.9] for all 3 viruses and RSV only, respectively. Subgroup analyses did not reveal benefits of ribavirin use in both acute (<30 days) and long-term (≥30 days) mortality for all 3 viruses.

Conclusion: Given the lack of effective antiviral therapy and significant mortality from RSV, HMPV, PIV infections in HSCTs/HMs, there is an urgent need for vaccine and antiviral agent development for these infections.

P126

Change in outcomes in patients with sepsis and haematological malignancy: 20 years of binational data

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Background: Sepsis profoundly impacts patients with haematological malignancy (HM). Treatment of HM has evolved rapidly, but changes in sepsis outcomes are not well defined.

Aims: To describe clinical characteristics and outcomes in patients with HM and sepsis admitted to an intensive care unit (ICU) in Australia and New Zealand (ANZ) from 2000-2019.

Methods: All adults admitted to ICU in ANZ from January 2000–December 2019 and meeting Third International Consensus Definitions for Sepsis (SEPSIS-3) were eligible for inclusion. Data were extracted from the ANZ Intensive Care Society Adult Patient Database (ANZICS-APD) and stratified into 5-year periods. Odds of in-hospital mortality between time periods were reported, using APACHE-III score to adjust for illness severity.

Results: Of 259,288 episodes of sepsis, 15,139 patients (5.8%) had HM. Patients with HM were less likely to have >/ = 1 chronic comorbidity (12 vs 24%) and more likely to have unknown source of infection (13% vs 5%). In-hospital mortality was higher for patients with HM than without (34% vs 18%, p <0.001). Mean age of patients with HM and sepsis increased over the study period (60 vs 65 years, p <0.001). In-hospital mortality for patients with HM and sepsis fell from 47% (2000-2004) to 29% (2015-2019) (p <0.001). Acute illness severity indices (APACHE III) declined over the study period. After adjusting for the change in illness severity, there was still a significant and progressive decline in the adjusted odds of death.

Conclusions: Outcomes have improved for patients with HM and sepsis admitted to ICU.

P127

Redirection of T cells via chimeric antigen receptor (CAR) to control the invasive fungal infections

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Invasive fungal infections (IFI) are associated with high rates of morbidity and mortality, and immunocompromised hosts are often affected. *Candida albicans* is among the main cause of IFIs in the last decades, and *Paracoccidioides brasiliensis* is found in most of the IFIs identified in the South America. *Rhizopus oryzae* causes mucormycosis that increased in the COVID-19 pandemic. Host immune response against IFIs depend of the effector activity of T cells, which is compromised in immunodeficient patients. However, chimeric antigen receptor (CAR) technology can redirect T cells to target any antigen inducing the cell activation, which can be applied in immunocompromised patient as done in cell therapy against cancer. We developed a CAR (M-CAR) specific to a carbohydrate on the fungal cell wall, and Jurkat cells expressing M-CAR after lentiviral transduction using a multiplicity of infection (MOI) of 1, 3, 5 or 10 had its recognition capacity evaluated against *C. albicans, P. brasiliensis,* and *R. oryzae*. CAR expression increased in a MOI dependent-manner, and M-CAR Jurkat cells produced high levels of IL-2 in the presence of hyphae form of *C. albicans,P. brasiliensis* yeast, and *R. oryzae* spores. These findings evidenced the capacity of M-CAR to recognize these fungi inducing T cell activation. This work opened new perspectives to evaluate the fungicidal activity of human T and NK cells expressing M-CAR in response to species of fungi studied.

Keywords: Chimeric Antigen Receptor (CAR), T cells, invasive fungal infections

P128

A call for attention: invasive pulmonary aspergillosis in patients with solid tumors

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Background: Invasive pulmonary aspergillosis (IPA) is a serious infection that affects immunocompromised patients. There are only small series of cases in patients with solid tumors (ST). The most frequent underlying disease described being lung cancer or pulmonary metastasis. Few cases have been described in patients with other malignancies or receiving target therapy for ST.

Aim: To describe the cases of IPA in patients with ST

Methods: Retrospective observational cohort study, performed in patients with ST complicated with IPA in an Oncology Hospital. Cases were detected through microbiology records. Diagnosis was made following EORTC/MSG criteria.

Results: Three cases of IPA (2 probable and 1 proven) were diagnosed in patients with ST (2017-2021). Underlying diseases were colorectal in 1 and breast cancer in 2. All were immunocompromised,1 received corticosteroids and 2 target therapy with palbociclib plus letrozole. All had underlying lung condition, COPD in 2 and lung metastasis in 1. None were neutropenic. Chest CT findings at diagnosis of IPA: 2 had interstitial lung infiltrates and nodular lesions (1 with cavitation), the other had hydropneumothorax. GM in BAL was negative in 2/2. *Aspergillus fumigatus* was isolated from BAL in 2 and from pleural fluid in 1. At 6 weeks 2 patients were alive and one died related to the infection

Conclusions: Patients with ST are an emerging group at risk for IPA. Diagnosis is difficult as IPA images overlap with progression of the underlying disease. High index of suspicious is advised in patients with ST that receive target therapy

P129

The role of regulator of G-protein signaling (Rgs)-1 in CD8+ TRM-cell mediated intestinal immunity

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Background: The gene encoding regulator of G-protein signaling 1 (*Rgs1*) is one of the most up-regulated genes in tissue-resident (T_{RM}) cells. Rgs1 inhibits signal transduction by increasing the GTPase activity of the Gαi protein subunit, which may attenuate chemokine receptor-mediated immune cell trafficking. Intriguingly, there is a striking genetic association of Rgs1 SNPs with T cell-mediated autoimmune disorders in patients (e.g., celiac disease, multiple sclerosis).

Aim: Herein, we investigate the ill-defined role of Rgs1 in T_{RM} cell differentiation and maintenance in the small intestine.

Method: A novel Rgs1-tdTomato reporter mouse confirmed the preferential Rgs1 expression in T-cell subsets in the intestinal mucosa under homeostatic conditions. To assess the impact of Rgs1 on the generation and maintenance of CD8 T_{RM} cells in the intestine, we used an adoptive co-transfer of congenic Rgs1$^{-/-}$and Rgs1$^{+/+}$ OT-I CD8^{+} T cells following local infection with *Listeria monocytogenes (Lm)-Ova*.

Results: During the acute phase of intestinal infection with *Lm-Ova*, Rgs1$^{-/-}$ OT-I T_{RM} cells became underrepresented in the small intestinal epithelium and lamina propria, which persisted throughout the memory phase (day 30 post-infection). Upon reinfection, intestinal Rgs1$^{-/-}$ OT-I T_{RM} showed an impaired capacity to limit the dissemination of potential pathogens to extra-intestinal organs.

Conclusions: These experiments reveal the critical requirement of Rgs1 for the local accumulation of CD8^{+} T_{RM} cells and the efficient T cell-dependent immunoprotection from systemic dissemination of pathogens upon reinfection.

P130

A multi-centre national study of COVID-19 infection in cancer patients

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Background & aims: COVID19 disproportionately affects the immunosuppressed, but its epidemiology over time is incompletely characterised. We describe Australian experiences of COVID19 in a national observational study of patients with malignancy.

Methods: An ongoing multisite prospective cohort study of adult COVID19 patients with active cancer was conducted. Clinical and laboratory data over 28 months (1/3/20-22/7/22) was collated from 15 hospitals.

Results: There were 491 patients included. Patients were a median of 63(IQR:50-71) years with majority male (254,52%). Solid organ

malignancy was most common (296,60%), followed by haematological malignancy (180,37%), then both (15,4%). Most common solid tumour was breast cancer (74/296,25%); most common haematological cancer was lymphoma (102/180,57%). Majority (275,56%) were undergoing cancer treatment at COVID19 diagnosis.

From 2020-2022, patients presented less with lower respiratory tract infections (57%,36%,5%) with increasing outpatient management (26%,50%,67%). Improved mortality was seen (27%,19%,11%). Median inpatient length of stay was 8(4-11) days. Intensive care admission was low (21,4%).

For patients who had repeated respiratory PCR testing, median time from first to last positive test was 17(7-25, n = 123) days. Cancer treatment modification occurred in 18(4%) and delay in 74(15%).

Conclusion: Despite improvements in outcomes, COVID19 still results in morbidity with impacts on cancer treatment. This preliminary data shows that cancer patients remain a vulnerable group and should be prioritised for public health interventions.

P131

Attenuated COVID-19 vaccine immunogenicity and risk factors in hematopoietic stem cell transplant recipients: a systematic review and meta-analysis

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Background: Hematopoietic stem cell transplant recipients (HSCTs) may experience the diminished immunogenicity to COVID-19 vaccines.

Aim: To summarize current evidence on COVID-19 vaccine responses and risk factors for their attenuation in HSCTs.

Methods: A literature was systematically searched and reviewed from the existence of databases through June 22, 2022. Descriptive statistics and random-effects model were used for a meta-analysis.

Results: From 46 studies, representing 4446 HSCTs, the weighted mean (95% confidence interval [CI]) of positive antispike seroconversion after COVID-19 vaccines was 40% (30%-51%), 80% (77%-83%), and 80% (69%-88%) for 1, 2, and 3 doses, respectively. The cellular immune response was 58% (40%-75%) after 2 doses. Notably, the risk factors (pooled odds ratio [95% CI]) for poor antibody response after 2 vaccine doses comprised recent rituximab exposure (0.10 [0.02-0.57]), haploidentical allografts (0.49 [0.28-0.87]), post-HSCT duration less than 24 months (0.22 [0.07-0.71]), lymphopenia (0.27 [0.16-0.45]), hypogammaglobulinemia (0.32 [0.22-0.47]), concomitant chemotherapy (0.48 [0.29-0.78]), immunosuppressants (0.22 [0.14-0.34]) and corticosteroids (0.29 [0.16-0.53]). Ongoing immunosuppressants (0.06 [0.00-0.81]) also increased risk of poor cellular immunogenicity.

Conclusion: In HSCTs, humoral and cellular immunogenicity to 2-3 doses of COVID-19 vaccines are attenuated by several risk factors. Further efforts on COVID-19 prevention including neutralizing monoclonal antibody uses are needed for this vulnerable population.

P132

Progressive course of alveolar echinococcosis in an immunocompromised patient treated with infliximab

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Background: Human alveolar echinococcosis (AE) is a zoonosis caused by the larval forms of *Echinococcus multilocularis* tapeworms with potentially increasing importance among immunocompromised patients.

Case presentation: A 70-year-old male diagnosed with rheumatoid arthritis in 2008 was initially treated with prednisone, methotrexate, leflunomide, etanercept, and since 2014 with anti-TNF agent infliximab. Abdominal MSCT was performed due to a pathologically changed liver findings on the regular ultrasound verifying an inhomogeneous formation of the right lobe (16 x 6.8 cm) with the additional change of the I liver segment, a necrotic infiltrate preaortally, 7 x 5 cm, affecting the celiac trunk and right adrenal gland; differential diagnosticly cholangiocarcinoma. The ultrasound findings 4 years earlier were described as normal. Liver punctate cytology showed tiny scolex hooks, which raised the suspicion of echinococcal disease, additionally confirmed by positive serology (IHA). PCR was successfully used for the amplification of *E. multilocularis* specific DNA fragments in tissue biopsy. Although antiparasitic therapy was started, the effect of albendazole is expectedly lower in AE and surgery is necessary. Due to the significant extension of AE and the impossibility of radical resection, liver transplantation is indicated.

Conclusion: The presented case suggests the need of high clinical suspicion, early diagnosis and treatment of emergent parasitic infections, manifesting a particularly severe clinical features in a growing number of immunocompromised patients.

P133

Invasive mucormycosis in patients with hematologic diseases: A single center 11-year experiences

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Background: Invasive mucormycosis (IM) are increasing with profound immune suppression.

Aims: The aim of this study was to determine the characteristics and outcomes of IM in patients with hematologic diseases.

Methods: We retrospectively reviewed all consecutive proven/probable IM cases between Jan. 2011 and Mar. 2022 in a cohort of IFD at Catholic Hematology Hospital, Seoul, Korea.

Results: A total of 44 (36 proven and 8 probable) cases of IM were identified. Most common underlying diseases were AML (n = 17), followed by ALL (n = 9). Primary infection site was lung (n = 30), paranasal sinus (n = 8), intestines (n = 4), and skin and soft tissue (n = 2). Disseminated infection was found in 27%. There were 16 isolates from 15 culture-positive IM patients; *Rhizopus sp.* (n = 4), *Rhizomucor sp.* (n = 4), *Cunninghamella sp.* (n = 3), *Paecilomyces sp.* (n = 3), *Lichthemia sp*. (n = 2). Coinfection with IA was found in 25% of patients. Surgery was performed in 75%. Survival rate at 42d and 100d were both 66%, while overall death was 27% with 7% of follow-up loss. Surgery was performed in 42% and 86% in deceased and survivor group at 6wks. Fifteen received subsequent chemotherapy or HSCT after the diagnosis of IM. Among them, 11 were successfully treated, while 4 died from other infectious complication. Two patients started chemotherapy within one month from the surgery, who recovered without any complications.

Conclusions: Culture-positive IM consists in 34% of IM. Coinfection with IM and IA is not rare. In cases with successful surgical resection of IM, subsequent chemotherapy or HSCT can be considered.

P134

Plastic antibodies for virus detection- VLP model

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Viral detection is a rapidly growing field owing to its increasing prevalence and ongoing evolution of viral variants and drug resistance. Molecular imprinting technology, made possible to produce tailor-made artificial receptors, also called plastic antibodies. The molecular imprinting process involves three main steps: self-assembly of template with functional monomer molecules, polymerization of tem-

plate-monomer complex, and template removal. The last step enables the unveiling of the binding cavities that are specific to the imprinted molecule and allows its rebinding.

In this under development work, we use Qβ VLP´s, which mimic viral particles, with dopamine as monomeric structures to make the imprinting sites on commercially available carbon screen printed electrodes (SPE). Using electrochemical impedance spectroscopy and fitting the Nyquist plots with a Randall's circuit, it is possible to follow and quantify (Ω) the modifications on SPEs.

VLP's are embedded into a 0.5mM dopamine monomeric solution and polymerization is electrochemically induced. The removal step is being optimized using a 0.6M Urea solution. Vlp's template rebinding step promotes surface charge differentiation that is seen in the impedance spectra at VLP concentration of 100pg/mL. Although sensor has shown sensitivity, sensor assembly still requires optimization due to unspecific adsorption of VLp's in the polymeric matrix.

Overall, this is a re-emerging technology now made possible due electronics advance. Measurements can be performed in situ with hight accuracy and giving immediate results.

P135

Comparison of BK virus (BKV) replication in the first year of lung (LT) and kidney (KT) transplantation. Results of a prospective study

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BKV reactivation is a cause of renal dysfunction in the first year after KT. Cases of BKV associated nephropathies (BKVAN) with renal failure have been reported in LT recipients (LTR), however the clinical impact of BKV replication after LT is unclear.

The aim of the study was to compare the incidence of BKV replication in LTR and in KTR and to explore the natural course of this replication in LTR for whom BKV monitoring was non interventional.

We prospectively measured plasma BKV DNA, 1, 2, 3, 6, 9 and 12 months after transplantation, in 297 patients who underwent kidney (n = 195) or lung (n = 102) transplantation in the University of Montreal hospitals between 2018 and 2020.

BKV replication was detected in 17% of LTR and in 30,25 % of KTR. It occurred within the first 3 months in 94% of LTR and in 64% of KTR. The median peak viral load was 422 copies/ml (range 23-79683 copies/ml) in LTR and 4770 copies/ml (range 26-954 000 copies/ml) in KTR (p = 0,0258). Viremia was sustained in 64,7% of the LTR and 66,1 % of the KTR. At month 12, nine LTR were still viremic (median 2290 copies/ml, range 23-126 240 copies/ml) and estimated glomerular filtration rate was not different in LTR with or without viremia

In summary, BKV replication was detected early after LT, with a lower incidence and viral load than after KT and without any impact on the renal function at one year after transplantation. Our results do not support the need for a systematic monitoring of BKV in the first year after LT to prevent BKVAN.

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Construction and characterization of a panel of immortalized natural killer cell lines expressing allelic variants for FCGR3A

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NK cells exert direct and antibody-dependent cytotoxicity (ADCC) via engagement of IgG-coated target cells by Fc-gamma receptor 3A (CD16). FCGR3A gene allelic variants are presumably involved in a wide-range of diseases and responses to monoclonal antibody therapy. Particularly, single-nucleotide polymorphism (SNP) V158F and L48H/R alter CD16's affinity for IgG but their impact on ADCC warrants further analysis.

Aims: To generate a panel of NK92 cell lines stably expressing L48H/R and V158F polymorphisms' combinations for FCGR3A, and test them in ADCC and direct cytotoxicity assays.

Methods: NK92 cells were transfected by electroporation. The mRNA and surface CD16 expression were analyzed by sequencing and flow cytometry, respectively. ADCC was tested using anti-CD20 or anti-EGFR antibodies, and Daudi, Raji and A431 as targets. Direct cytotoxicity assays were performed using the K562 cell line as targets.

Results: We engineered six different NK92 cell lines. CD16 expression was stable over time. The monoclonal antibody-induced ADCC was dose-dependent. There was no significant difference in ADCC between the NK92 transfectants regardless of the genetic variants involved. The NK92LL_VF transfectant showed the highest direct cytotoxicity for all E:T ratios tested; whereas NK92RR_VV showed a trend of lower killing, even lower than wild-type NK92 cells lacking CD16 (controls).

Conclusions: We developed a reliable tool for analyzing human NK cytotoxicity without the need to purify primary NK cells. NK92 transfectants similarly performed ADCC, regardless of the polymorphisms. However, R homozygosity (L48H/R) showed lower direct cytotoxicity against K562 cells compared to the other NK92 transfectants. This finding is currently under examination.

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