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## Highlights

# We refuse to die – T cells causing havoc

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### ABSTRACT

This issue of the *Biomedical Journal* offers insights into the origin and consequences of different lymphoproliferative disorders and autoimmunity. Furthermore we learn about RASopathies, a group of congenital disorders that occur rather frequently. Then the current ELISA assays for measuring antibody avidity are critically examined, the relationship between female sex steroid hormones and cardiovascular disease is explored, and an assessment of persistent diarrhea as a leading cause of child death in India is performed. Additionally, there are several articles about COVID-19, presenting its connection to neutrophil recruitment and acute respiratory distress syndrome, as well as its relation to changes in the vascular glycocalyx. A COVID-19 case study from the emergency room is presented. We are also introduced to novel treatment approaches against COVID-19 like the construction of peptide-based vaccines, or targeting the respiratory tract microbiome. Finally, there is an assessment about how prepared medical students at a Taiwan University feel for independent practice, and another article about the treatment of intravascular large B cell lymphoma in a Taiwanese institution. Lastly, we discover possible surgery techniques in the case of external auditory canal osteoma.

## Spotlight on reviews

### We refuse to die

In Dan Harmon's Emmy awarded animation series *Rick & Morty*, the mad scientist Rick Sanchez unleashes Mr. Meeseeks. Mr. Meeseeks are blue creatures only called to life to fulfill one purpose. Upon completion of their task they will be removed from existence. Through various mishaps however, Mr. Meeseeks do not vanish and instead more and more of its kind are created until the blue clones clog up the entire house. They cause havoc due to their sheer number, thus causing harm to those they swore to serve.<sup>1</sup>

Similarly, in healthy individuals T cell activation induces the expression of the death receptor ligand FASL that eventually allows for T cell apoptosis. When this system fails, expansion of autoreactive T cells occurs which may lead to an autoimmune disease [1]. Such autoimmune disorders appear to be manifold in regards to aspects like demographics and primary manifestation. However, it is hypothesized that there are common genetic risk factors for various autoimmune diseases [2].

In this special issue of the *Biomedical Journal* four intriguing reviews concerning the rare pediatric Autoimmune Lymphoproliferative Syndrome (ALPS) and ALPS-like disorders are presented.

In ALPS, mutations affecting the FAS pathway, namely the death receptor CD95 itself as well as its ligand, are one factor

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<sup>1</sup> [https://rickandmorty.fandom.com/wiki/Mr.\\_Meeseeks](https://rickandmorty.fandom.com/wiki/Mr._Meeseeks), last access: 2021/08/28.

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leading to the syndrome. FAS is essential for eliminating autoreactive lymphocytes [3].

Magerus et al. review the somatic and/or germline mutations – both homozygous and heterozygous – in mice models as well as humans that influence the FAS pathway. They also have a closer look at inherited non-FAS mutations that play a part in ALPS. Finally, they suggest that a second event next to any mutation affecting the FAS induced apoptosis might be involved in ALPS onset [4].

#### James Bond: “When I kill, it is on specific orders”

60 years ago, in August 1961, the famous Checkpoint Charlie in Berlin, Germany, was set up. It was part of the then freshly established Berlin wall that would separate East and West Berlin for the following 28 years.<sup>2</sup> The checkpoint became a spotlight for various political scandals and would also pose as a scenery for heated up emotions in famous spy movies like James Bond, Octopussy.<sup>3</sup>

Immune checkpoints on the other hand also become scandalous when deficient. Interactions between FAS and its ligand are for instance tightly regulated due to their ability to permanently eliminate cells via apoptosis [5].

Gómez-Díaz et al. compare the biological mechanisms of ALPS with two other, rare, monogenetic disorders that are characterized by a clinically overlapping phenotype: Cytotoxic T Lymphocyte Antigen 4 (CTLA-4) insufficiency due to heterozygous mutations, and Lipopolysaccharide Responsive Beige-like Anchor (LRBA) protein deficiency as a consequence of biallelic mutations. Both checkpoint deficiencies lead to a defective suppressive activity of regulatory T cells (Tregs). Approaches to the differential diagnosis are analyzed as to distinguishing between the disorders that might otherwise clinically present in a similar fashion. Finally, specific treatment options are elaborated on [6] [Table 1].

#### One to rule them all

Next to the previously mentioned checkpoint deficiencies, defects in other pathways may lead to ALPS-like disorders, all while presenting regular apoptotic processes.

Upon binding of a cytokine or growth factor to its receptor, the JAK-STAT pathway is activated. In mammals, four JAKs and seven STATs can thus be employed by more than 50 cytokines in various combinations [7], leading to a plethora of pathways involved in proliferation, differentiation, migration, inflammation and apoptosis [8]. Especially the signal transducer and activator of transcription 3 (STAT3) is a key actor in vertebrate development and mature tissue function like immunity. Mutations of STAT3 with the consequence of its inactivation or hyperactivation lead to human disease [9].

Faletti et al. summarize their current understanding of germline STAT3 gain of function (GOF) mutations that affect all parts of the protein and are associated with autoimmunity

as well as lymphoproliferation. They discuss molecular mechanisms, the challenging diagnosis due to lack of a specific test routine and available treatment possibilities of the autosomal-dominant inborn error of immunity [10].

#### Fatal consequences

In many countries, abortions are strictly regulated and have repeatedly been subject of heated discussions and politically motivated riots. Around the turn of the year 2020/2021, Poland was shook by partially violent protests against their new abortion laws that came into place in January 2021. Among other things, abortions due to fetal defects are now prohibited. At the same time, fetal defects were the main reason for legal abortions in Poland in 2019 (1074 out of a total of 1110 abortions) [11].

The congenital disorders comprised under the term RASopathies occur in about 1 of 1000 live births, thus representing one of the largest groups of developmental disorders. Around 20 disease genes have been identified, which almost all encode proteins involved in the RAS/MAPK signaling pathway. The RAS/MAPK cascade is ubiquitous and *inter alia* involved in proliferation, survival and differentiation [12]. Mutations in the pathway can entail ALPS-like syndromes, as reviewed by Riller and Rieux-Laucat in a fourth article of this special issue. The authors scrutinize eight RASopathies that result of germline mutations in the RAS/MAPK pathway. They further discuss somatic mutations affecting the RAS/MAPK cascade that have overlapping phenotypes to the germline mutations, leading to cancers and hematopoietic events. Riller et al. conclude that new technologies like single-cell epitope and transcriptome analysis will allow for a better understanding of the consequences RAS/MAPK gain of function mutations have [13].

## Also in this issue

### Editorial

Rieux-Laucat, Kanellopoulos and Ojcius offer a comprehensive introduction to the four articles about mutations related to the autoimmune lymphoproliferative syndrome (ALPS) and ALPS-like syndromes. All articles underline the impact somatic mutations exert as causing or contributing factors to autoimmunity disorders, finally guiding our understanding for a need of specific and personalized treatment approaches [14].

### Reviews

#### Same same but different

The development of the Enzyme-Linked Immunosorbent Assay (ELISA) was revolutionary for the research of antigen antibody interactions. Previously, scientists were conducting a radioimmunoassay that evidently brought its own set of challenges in terms of safety and waste disposal. The ELISA hence rapidly gained track since the 1970s and still finds large application in analytical and clinical investigations [15].

Correa et al. review the application of ELISA methods to determine antibody avidity. They criticize the lack of

<sup>2</sup> <https://www.vWoStberlin.de/en/checkpoint-charlie>, last access: 2021/08/28.

<sup>3</sup> <http://www.jamesbondmm.co.uk/locations/checkpoint-charlie>, last access: 2021/08/28.

**Table 1 Characteristics of ALPS, CTLA-4 insufficiency, and LRBA deficiency.**

PID	ALPS-FAS/ALPS-FasL	CTLA-4 insufficiency	LRBA deficiency
Characteristic			
Gene affected	TNFRSF6 (FAS)/FAS-L	CTLA-4	LRBA
Hereditary pattern	germline or somatic, AD or AR	germline, AD	germline, AR
Penetrance	Missense mutations in intracellular domain: 90% Truncated mutations in intracellular domain: 70% Any mutation in extracellular domain: 30%	Incomplete (70%)	Almost complete (Only one individual stayed healthy)
Genotype-phenotype correlation	Yes (Heterogeneous syndrome)	No (Heterogeneous syndrome)	No (Heterogeneous syndrome)
Onset	Neonatal	Early adulthood	Childhood
Autoimmune cytopenias	Yes	Yes	Yes
Enteropathy	Not frequent	Yes	Yes
Organomegaly	Yes	Yes	Yes
Hypogammaglobulinemia	Few cases; mostly hyper-IgG and hyper-IgA.	Yes (around 80%)	Yes (around 60%)
Recurrent infections	Not frequent (mostly bacterial infections)	Yes (not to a specific pathogen)	Yes (not to a specific pathogen)
Lymphoproliferation	Yes	Yes	Yes
Endocrinopathy	No	Yes	T1DM, thyroiditis
Main laboratory findings	Increased circulating DNT cells	Decrease of CTLA-4 expression	Decrease of T regs (~60% patients)
	Increased plasma levels of FasL	Abnormal CTLA-4 transendocytosis	Decreased switched B cells
	Increased plasma levels of IL-10	Increase of CD21 <sup>low</sup> B cells	Decreased plasmablasts
	Decrease in vitro T-cell apoptosis	Increased DNT cells	Decreased CTLA-4 expression Decreased CTLA-4 transendocytosis Absence of LRBA expression
Mimics murine model	Yes	No	No

Source: Gamez-Diaz et al. [6]. Abbreviations: AD: Autosomal dominant; AR: Autosomal recessive.

standardization of the various commercial kits and in-house methods. Thus, the reliability of the assay becomes questionable and the results of different protocols are not comparable. Correa et al. state that not all ELISA methods are suitable for determination of antibody avidity. Additionally, the binding reaction depends on numerous factors like the plate material, pH, incubation conditions, concentrations and more. In the review, Correa et al. hence suggest using universal parameters and a modified ELISA that is based on the indirect ELISA method [16].

#### *Breath-taking dance on a tightrope*

In 2021 the COVID-19 pandemic still keeps the entire world on the tips of its toes. Although large efforts are made to continuously learn more about the virus and possible prevention and treatment, the WHO currently reports more than four million deaths worldwide due to COVID-19.<sup>4</sup>

Following the infection with SARS-CoV-2, individuals may develop Acute Respiratory Distress Syndrome (ARDS). This is due to the damage done to the lung tissue by the COVID infection, which results in the recruitment of large amounts of immune cells. A cytokine storm results as a consequence of immune cell accumulation [17].

Neutrophils are quickly recruited to sites of inflammation in the lungs through chemoattractive signals. They usually have a short lifespan and neutrophil homeostasis is essential during an infection/inflammation, since neutropenia or on the other hand neutrophilia may entail dangerous ramifications

[18]. Especially a higher count of neutrophils in COVID-19 ARDS patients predicts a lethal outcome [19]. Yang et al. state that the role of neutrophils in ARDS is complex, since they participate in remodeling damaged lung tissue but also promote pulmonary inflammation, thus damaging lung tissue even further. The authors hence suggest targeting neutrophils as a potential treatment for ARDS as well as COVID-19, although this will require a fine balancing to not overshoot into either direction [17].

#### *Original articles*

##### *Constructing a new generation of vaccines*

Sarma et al. consider continuous efforts against SARS-CoV-2 as highly needed, especially because of its virulence. They suggest peptide-based vaccines as a superior approach, emphasizing that they are safer, less toxic and provoking less allergies than other vaccine types [20]. Additionally, peptide-based vaccines allow for easy introduction of chemical modifications [21].

Sarma et al. describe the use of immunoinformatics to predict B cell and T cell epitopes that are highly promising for peptide-based vaccine construction against SARS-CoV-2. After sequence retrieval, they performed an evolutionary and structural analysis and homology modelling. The final step they executed was the epitope prediction, either for linear or discontinuous epitopes for B cells, *vice versa* for the binding of T cells to human MHC I and MHC II. Sarma et al. successfully identified several promising B and T cell epitopes for antigenic SARS-CoV-2 protein [20].

<sup>4</sup> <https://covid19.who.int/table>, last access: 2021/08/28.

### Young at heart

The metabolic syndrome includes amongst other constituents central obesity, insulin resistance and increased risk of cardiovascular disease (CVD). Menopause as such increases the incidence of metabolic syndrome in women [22]. At the same time, CVD is the leading cause of death in people with type 2 diabetes [23].

Azizian et al. surveyed the influence of estrogen and/or progesterone on cardiovascular risk indices in female menopause model rats with type 2 diabetes. Female sex hormones act on their own in an anti-inflammatory manner, but Azizian et al. were especially interested in the combined use of estrogen and progesterone in contrast to a standalone application. Surprisingly, they found that the administration of estrogen and progesterone combined and the use of progesterone alone were ineffective in many cases. In opposition the administration of estrogen on its own demonstrated a cardiovascular protective effect [24].

### There's a new kid on the block

In 2019 the WHO estimated that 5.2 million children under the age of five died mostly from preventable and treatable causes. Some of the leading causes are birth complications, congenital anomalies and diarrhea.<sup>5</sup> Together with UNICEF the WHO hence set up a Global Action Plan to end preventable child deaths from pneumonia and diarrhea by 2025 [25].

Enteropathogenic *Escherichia coli* (EPEC) causes persistent diarrhea and is highly prevalent in community and hospital settings, thus infecting children worldwide [26]. Snehaa et al. set out to investigate the regional presence of EPEC in East Delhi, India, as EPEC often remains underdiagnosed in the country due to lack of a conventional identification tool. The research group recognized the alarming trend that there is a shift occurring from the typical to the atypical, drug resistant EPEC. This means that much more severe public health monitoring will be required to improve detection and consequently establish counter-measures [27].

### Intravascular large B cell lymphoma

Ong et al. dove into reporting the clinical features and outcome of intravascular large B cell lymphoma (IVLBCL) in a single institution of Taiwan. They retrospectively reviewed 12 patients that were newly diagnosed over the course of 12 years. Their study shows that the rituximab-based chemotherapy allows for considerable remission, although results might have been even more promising with earlier diagnosis and thus earlier treatment onset [28].

### Exploring surgery techniques

Bony outgrowths of the external auditory canal (EAC) are rare neoplasms, that grow slowly but can cause considerable damage in the long run like recurrent infections and hearing loss. Surgical removal is possible through post-auricular, endaural or a transcanal approach with each method comprising different advantages and disadvantages [29].

Chen et al. provide a study to research the feasibility of transcanal endoscopic ear surgery (TEES) for EAC osteoma. This method is minimally invasive. Twelve patients underwent a direct transcanal removal procedure without any postoperative complications. Three patients with broad base osteoma successfully underwent a TEES involving a skin flap [30].

### 3, 2, 1 - ready? Go!

Medical schools need to prepare their students for a broad spectrum of detailed knowledge. However, this may lead to better knowledge-based skills in opposition to confidence in the necessary competencies as an independent doctor. The curriculum is designed to allow a gradual building of clinical skills. However, the question is, whether medical students also feel ready to work as newly qualified doctors from a psychological point of view.

Yu et al. hence decided to assess preparedness of Taiwanese medical students in the final years of their study and rotation program. Their findings showed for the cohort that the preparedness for practice strongly depends on how medical undergraduates see themselves as medical professionals. Furthermore, the students were most prepared for self-directed learning although least prepared for interpersonal and patient management skills [31].

### Brief communication

#### *The myth of the sterile respiratory tract*

The upper respiratory tract as well as the lungs are not sterile, as some textbooks historically still claim. On the contrary, the moist and warm tissues are exposed to microbes from the oropharynx and from inhaled air. The local growth conditions for microbiota are overall heterogeneous. The presence of a lung disease however may drastically alter microbiome population dynamics [32].

Velmurugan et al. describe the bacterial dysbiosis due to SARS-CoV-2 in the upper respiratory tract by analysis of RNA sequencing of infected ferrets. A large reduction in beneficial bacteria responsible for coordination of the lung–gut axis can be observed. To reverse the dysbiosis, Velmurugan et al. suggest the development of specific therapeutics against COVID-19 like antibiotics or bacteriophages. Additionally, commensal and beneficial bacteria could be recovered by nasal administration of according probiotics [33]. Finally, the respiratory microbiome is not only influenced by disease, but also by various factors such as ageing and lifestyle habits like smoking [34].

#### *Running against the clock*

The fight against COVID-19 often is a run against time for frontline healthcare workers. The pandemic relentlessly challenged health care systems around the world and continues to do so. In order to deal with the health crisis, numerous flexible adaptations had to be made, more use of telemedicine, different ways of teamwork and organization of access to hospital spaces are just a few of them [35].

The current situation constitutes a continuous learning process. This unfortunately also means that at times critical situations may not yet be handled seamlessly.

<sup>5</sup> <https://www.who.int/newsroom/factsheets/detail/childrenreducingmortality>, last access: 2021/08/28.

Tsai et al. describe a case of a 38-year-old patient in the emergency department with dyspnea. While waiting for the COVID-19 test results, hence delaying the treatment of other possibly serious disorders, the patient experienced respiratory failure and cardiac arrest. Tsai et al. emphasize that safety of the patient as well as the clinician needs to be considered and advises the use of proper protective care for medical staff during the care or interventions in times of the pandemic [36].

### Letter

#### COVID-19 and the vascular glycocalyx

In a previous issue of the *Biomedical Journal*, a review by Yamaoka-Tojo was published about the mechanisms of vascular endothelial glycocalyx degradation in COVID-19 patients. Yamaoka-Tojo elucidated that the mortality associated with COVID-19 is increased with the presence of various comorbidities like hypertension, diabetes, COPD, and cardiovascular disease. At the same time, those comorbidities are correlated to the pathophysiology causing damage to the vascular endothelial glycocalyx. Yamaoka-Tojo suggested several possible therapeutic targets to address COVID-19 while focusing on the vascular endothelial glycocalyx [37].

In response to this article, Tricarico and Travagli agree and add food for thought. The abnormal recruitment of elements like lymphocytes and the following cytotoxic consequences are correlated to the morphological variations of the glycocalyx. Understanding the mechanisms behind it would allow to efficiently personalize treatment options, although Tricarico et al. make it clear, that the reduction in glycocalyx cannot serve as only explanation for the parenchymal damage [38].

### Conflicts of interest

The author declares no conflicts of interest.

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