Immune response to SARS-CoV-2

○Akiko Iwasaki
Yale University School of Medicine, HHMI

The clinical presentation of COVID-19 involves a broad range of symptoms and disease trajectories. Understanding the nature of the immune response that leads to recovery over severe disease is key to developing effective treatments for COVID-19. In this talk, I will discuss immune responses in COVID-19 patients with moderate and severe disease. I will compare viral load, immune phenotype and cytokines that are predictive of mortality, and discuss signatures of cytokines and growth factors that associate with recovery vs. disease exacerbation. I will also discuss sex differences in immunity to SARS-CoV-2 and how such differences correspond to disease outcomes.

Immunological memory to SARS-CoV-2 over six to eight months after infection

○Alessandro Sette[1,2] Daniela Weiskopf[1] and Shane Crotty[1,2]
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Understanding immune memory to SARS-CoV-2 is critical for improving diagnostics and vaccines, and for assessing the likely future course of the pandemic. We analyzed multiple compartments of circulating immune memory to SARS-CoV-2 in 185 COVID-19 cases, including many cases at ≥ 6 months post-infection. Spike IgG was relatively stable over 6+ months. Spike-specific memory B cells were more abundant at 6 months than at 1 month. SARS-CoV-2-specific $CD4^+$ T cells and $CD8^+$ T cells declined with a half-life of 3-5 months. By studying antibody, memory B cell, $CD4^+$ T cell, and $CD8^+$ T cell memory to SARS-CoV-2 in an integrated manner, we observed that each component of SARS-CoV-2 immune memory exhibited distinct kinetics.

COVID-19: Prevention and control in China and vaccine development

○George F. Gao
Chinese Center for Disease Control and Prevention

As of 1 November, nearly 46 million cases and 1.2 million deaths have been reported globally. COVID-19 has been a global health threat and important factor that would impact the economic and social life worldwide in the long-term. How did China achieve the containment of Wuhan outbreak, the following seven interventions were very important, which included detection, isolation and quarantine of cases and close contacts, social distancing, movement restriction, personal protective measure, social mobilization, infection prevention and control, environment measures. Of them, active case finding and management is the core measure, which means to test each suspected case, to isolate and manage each case and to trace and quarantine each close contact. Also an effective commanding system led by State Council is crucial. Now most areas of mainland China are virus-free and keep the containment status, so precise COVID-19 response strategy is very important to balance the COVID-19 response and socioeconomic development. Now we implement Aggressive Defense Strategy at New Normal stage. The two focus include continuously and forcefully prevent importation and implement the strategy of "protracted game of whack-a-mole" or "fire blanket strategy" to stem domestic epidemic resurgence. We should not only prevent imported by person but also imported by contaminative cold food products. The key interventions without specific antivirals and vaccines are non-pharmaceutical interventions. The key point of current COVID-19 response and control in China include the following aspects: early detection of epidemic and early response, science-driven risk community classified and risk area control, outbreak prevention and control in high risk places, strong normalization response of high risk area, actively community mobilization and response, and powerful command and support system. Vaccines are urgently needed to control the COVID-19 pandemic and to help the return to prepandemic normalcy. A great many vaccine candidates are being developed globally, some of which have entered clinical trials. In this presentation, I will introduce the development of COVID-19 vaccines, in particular, for those under clinical evaluation in China, including an inactivated virus vaccine, BBIBP-CorV and a protein subunit vaccine, ZF2001.

Development of DNA vaccines targeting SARS-CoV-2

○Hironori Nakagami
Osaka University

To fight against the worldwide COVID-19 pandemic, the development of an effective and safe vaccine against SARS-CoV-2 is required. We designed plasmid DNA vaccine targeting the SARS-CoV-2 Spike glycoprotein (S protein) as pandemic vaccine, and the humoral, cellular, and functional immune responses were characterized to support proceeding to initial human clinical trials. After intramuscular injection or intradermal injection with needleless injector of DNA vaccine encoding S protein (three times at 2-week intervals), the humoral immunoreaction, as assessed by anti-S protein or anti-receptor-binding domain (RBD) antibody titers, and the cellular immunoreaction, as assessed by antigen-induced IFNγ expression, were up-regulated. We also confirmed the neutralizing action of DNA vaccine-induced antibodies. In IgG subclass analysis, IgG2b was induced as the main subclass. Based on these analyses, DNA vaccine with alum adjuvant preferentially induced Th1-type T cell polarization. Further B cell epitope mapping analysis using a peptide array showed that most vaccine-induced antibodies recognized the S2 and RBD subunits. In conclusion, DNA vaccine targeting the spike glycoprotein of SARS-CoV-2 might be an effective and safe approach.

Nucleic acid-based immuno-prophylaxis and -therapy against COVID-19; haste makes waste

○Ken J. Ishii
Division of Vaccine Science, The Institute of Medical Science, The University of Tokyo / Mock-up vaccine project, Center for Vaccine and Adjuvant Research, National Institute of Biomedical Innovation, Health and Nutrition / Laboratory of Vaccine Science, Immunology Frontier Research Center, Osaka University

Nucleic acids are an attractive molecule for both vaccine vector and immunotherapeutic agents. It is because 1) nucleic acids are easy to produce large amount relatively in a short time of period, and relatively simpler and cheaper than those produced as viral or bacterial vector or recombinant proteins. Synthetic DNA and RNA are also as an alternative immunotherapeutic for natural compounds such as cell wall extracts and purified components of bacteria and fungi.
While DNA vaccines have been used in animals and human, capable of priming humoral and cellular immune responses to the encoded antigen (Ag), their ability to induce Ag-specific CD8+ T cell responses remain lower than expected. Among the strategies for improving DNA vaccine immunogenicity are booster vaccinations, alternate vaccine formulations, electroporation and genetic adjuvants, but few, such as extracellular vesicles (EVs), target natural Ag delivery systems. I will present and discuss in detail about the results obtained by DNA vaccination targeting EV. In addition, we are currently developing mock up vaccines based on mRNA and lipid carrier, which seem better than conventional DNA vaccinations. I will try to introduce our new data for COVID-19, if possible.
Clinical trials using immunostimulatory DNA or RNA, particularly agonistic as well as non-agonistic ligands for Toll-like receptors (TLRs) and stimulator of interferon genes (STING), have revealed their therapeutic potential not only as vaccine adjuvants but also as mono-immuno-therapeutic agent such as an anti-tumor agent. I will overview the relevant R&D against viral infections. We will discuss about new data obtained by various candidates for next generation DNA/RNA vaccine, nucleic acid adjuvants including K/D type humanized CpG ODN and unique STING ligands, such as nanoparticle using non-agonistic Dectin-1 ligand.

Cytokine storm and related diseases

Moderators: Hisashi Arase and Sujin Kang

The pandemic coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a serious global health threat. SARS-CoV-2 infection is associated with a high risk of mortality, causing severe respiratory failure, cardiovascular complications, and in some cases, affecting the nervous and mucosal systems. Immunological analysis of COVID-19 patients shows that SARS-CoV-2 infection elicits a cytokine storm, suggesting possible efficacy of anti-cytokine therapies. This session will highlight the recent basic scientific breakthroughs in our understanding of the pathogenesis of COVID-19 and related inflammatory diseases and focus on the development of new therapeutics for COVID-19. Recent mechanistic insights into inflammatory airway disease and their relevance to progressive lung diseases following respiratory viral infection (including COVID-19) poses a particularly timely subject deserving of urgent attention. We anticipate that the discussions during this session will serve to deepen our understanding of COVID-19 and look forward to your active participation.

Interleukin-6; From Arthritis to CAR-T and COVID-19

○Tadamitsu Kishimoto
Immunology Frontier Research Center, Osaka University

Blockade of IL-6 function by anti-IL6R antibody（Tocilizumab or Actemra）has been shown to be effective for the treatment of autoimmune inflammatory diseases including rheumatoid arthritis. Interestingly, Actemra rescued cytokine storm induced by CAR-T cell therapy. COVID-19 patients in the serious cases showed cytokine Release Syndrome (CRS) which suggested us that Actemra might be effective on the serious case of COVID-19. In this presentation, in the first part, I will summarize the therapeutic effect of Actemra for the disease induced by overproduction of IL-6. Then, I will talk to cytokine release syndrome by CAR-T cell therapy and COVID-19.

ACE2 – from fly hearts to the heart of a pandemic

○Josef penninger
Department of Medical Genetics, Life Sciences Institute, University of British Columbia, Vancouver, Canada / IMBA, Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria

My group the first ACE2 mutant mice which we initially identified studying fly heart development (Crackower et al. Nature 2002). We then developed ICUs for lung failure in mice which allowed us to show that ACE2 is the essential SARS receptor *in vivo* (Kuba et a. Nature Medicine) and that ACE2 protects from lung injury providing a molecular explanation why SARS-CoV and now SARS-CoV2 become lethal diseases (as compared to other Coronaviruses giving us the common cold) (Imai et al. Nature 2005). Over the years we also showed that ACE2 protects multiple tissues such as the heart, lung, kidney, or blood vessels from more serious disease and that ACE2 is also expressed in the kidney and the luminal surface of the gut epithelium (e.g. Danilczyk et al. Nature 2006, Hashimoto et al. Nature 2012, etc). Therefore, our previous work has provided critical insights and a blueprint for the current COVID-19 pandemic. I will discuss how this knowledge is being translated to clinical trials in severe COVID-19 patients and provide new data the use of organoids in SAR-CoV-2 infection and how glycosylation affects Spike binding at real-time, single molecule resolution.

Enhancement factors for SARS-CoV2 infection

○Hisashi Arase
Laboratory of Immunochemistry, Immunology Frontier Research Center, Osaka University / Department of Immunochemistry, Research Institute for Microbial Diseases, Osaka University

SARS-CoV2 causes severe pneumonia in certain patients, although infected patients do not always show severe diseases. Therefore, it is important to elucidate the factors that induce severe diseases in SARS-CoV2-infected patients. Spike glycoprotein of SARS-CoV-2 associates with the ACE2 on host cells and mediates membrane fusion with host cell membrane during infection. ACE2 is highly expressed on kidney and small intestine but ACE2 expression on lung is quite low. Therefore, there is a possibility that certain factors that enhance the SARS-CoV2 infection are involved in the severe pneumonia. In order to identify the enhancing factors for SARS-CoV2 infection, we have screened cDNA library from the lung as well as antibodies from infected patients. From these screening, we have identified possible factors that are involved in the enhancement of SARS-CoV2 infection to host cells. In this talk, I will discuss the function of these newly identified factors in severe pneumonia.

Establishment and Progress of Joint Research Coronavirus Task Force in Japan

○Takanori Kanai
Department of Gastroenterology, Keio University School of Medicine

Formerly known scientists in the fields of clinical genetics, genetic informatics, molecular oncology, basic and clinical immunology, and virology have come together to start COVID-19 research (Joint Research Coronavirus Task Force). It is great that we were able to gather together with a common passion to challenge this unknown enemy beyond academic groups and academic societies. Now, we are fighting day and night to clarify the question "Why do Japanese people have an extremely low mortality rate due to COVID-19?" in the activities of the Task Force. Fortunately, we were able to obtain large-scale research funding from the government, and above all, we received support from medical professionals, entrepreneurs, the media, and many hospitals fighting in the clinical setting of COVID-19 in the midst of the corona disaster. It is becoming a base for Japan's leading corona research, clinical data, and sample biobanks. The power to abandon and mobilize against enemies that may threaten the survival of homo sapiens shares a sense of exhilaration and mission that has never been experienced with members of the Task Force All the members of the Task Force think that "a pinch is an opportunity" based on "helping if there is a person in need", and through this corona host gene research, gather the stupid power and wisdom of the fire place to control the corona. Looking back on history, I hope that "pinch" (war and pandemic) will create scientific innovation, and that the battle with the new corona will bring new treatments through innovation, which will surely be overcome in the future. In this talk, I would like to introduce the establishment and progress of the Joint Research Coronavirus Task Force, as well as my personal views on the aspects of corona infection as an intestinal infectious disease and its cytokine storm prevention.

Dynamic changes in host nuclear system to virus infection

○Yumiko Imai
National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN)

Virus-host interaction controls immune and inflammatory responses in host, leading to the formation of severe pathology of infectious diseases. Here we focus on the dynamic changes in host nuclear system to influenza virus infection from the aspect of lipid metabolism and virus RNA transport as well as host chromatin 3D structures.

Review Talk and Panel Discussion

Current status and Mystery of Covid-19

Coordinator: Noriko Toyama-Sorimachi
Research Institute, National Center for Global Health and Medicine

Since the information about COVID-19 is easily available from everywhere, it is necessary for all of us to correctly understand the etiology and pathology of COVID-19 and to share the current problems, to eliminate the pandemic. In this session, first, Professor emeritus of Osaka University, Miyasaka Masayuki will give an overview talk about the current COVID-19 pandemic; so far what we know of and do not. After that, five scientists actively conducting the cutting-edge research on SARS-CoV2 or COVID-19 pandemic in Japan will discuss from the multiple aspects including SARS-CoV2 susceptibility between ethnic groups, the immune responses against SARS-CoV2 virus, and the current state of vaccine/therapeutics development and its problems (unsolved issues). This session will also discuss how immunologists and immunology research contribute to the fight against the emerging infectious diseases including SARS-CoV2, in the future.
Japanese language will be used in this session, and the English simultaneous interpretation will also be available. We will welcome as many questions and comments as possible, through chat function of Zoom. We look forward to your active participation.

Review Talk: Masayuki Miyasaka
IFReC, Osaka University, Japan

There is much controversy in the understanding of COVID-19, an infectious disease caused by a highly transmissible virus, SARS-CoV-2 that emerged in late 2019. A wide range of diverse and antagonistic opinions has been circulating, causing more confusion than clarity. For instance, “COVID-19 is highly pathogenic, probably causing tens of thousands of deaths in Japan in the absence of appropriate countermeasures”, “no, COVID-19 is a just a simple virus infection, not much different from that caused by influenza virus”. “Since COVID-19 should induce strong immunity once contracted, we should not worry about getting infected”, “no, COVID-19-induced immunity should wane rapidly, and there is no point of getting infected with this virus deliberately”. A more extreme and controversial opinion is, “herd immunity has already been generated, and hence, there will not be any more waves of infections in Japan”. So, what is correct and what is not…? In this review talk, I discuss the current COVID-19 research, with an emphasis on immune defense mechanisms against SARS-CoV-2.

Technical Seminar 1

Regulation of tissue specific inflammation via the IL-6 amplifier and gateway reflexes

○Masaaki Murakami
Division of Psychoimmunology, Institute for Genetic Medicine, Hokkaido University

We discovered two mechanisms that regulate inflammatory diseases: the IL-6 amplifier and gateway reflex in 2008 and 2012, respectively. The IL-6 amplifier is hyper NFkB activation machinery in nonimmune cells including fibroblasts and endothelial cells. It is activated by the simultaneous activation of NFkB and STAT3 in cells of the affected regions, enhancing the expression of NFkB targets such as cytokines, chemokines, and growth factors. Some disease-associated genes activate the IL-6 amplifier by enhancing the NFkB pathway in tissue-specific populations such as kidney tubular cells and keratinocytes. The gateway reflex, which is a new concept in the field of neuro-immune interactions, describes neural circuits that establish gateways for autoreactive T cells to enter organs that have bloodbarriers, leading to tissue-specific autoimmune diseases. Notably, the gateways are established at endothelial cells by sympathetic-mediated activation of the IL-6 amplifier. I will explain the IL-6 amplifier and the gateway reflex, beginning from their discoveries to recent advances with experiments using CytoFLEX and MoFlo Astrios.

Technical Seminar 2

Introducing New StarBright Dyes, New bright fluorescent nanoparticles developed for Flow Cytometry.

○Nobuyuki Nakata
Bio-Rad Laboratories

StarBright Dyes are generated from different monomers, modification of the polymerization process produces exacting excitation and emission characteristics with maximal brightness. StarBright Dyes are conjugated to our highly validated flow antibodies, and the brightness allows easy resolution of rare populations and low density antigens while maintaining the flexibility to fit to into any multicolor panel.

Technical Seminar 3

COVID-19: stimulation, analysis and safe sorting of rare antigen- and virus-specific T cells

○Marcello Stein and Felix Eppler
Miltenyi Biotec B.V. & Co. KG

Analysis of antigen- and virus-specific T cells is essential to the understanding of fundamental immunological processes in the contexts of e.g. infectious diseases, immuno-oncology, as well as immune tolerance.
In COVID-19, for instance, the presence of SARS-CoV-2 reactive T cells indicates an infected or convalescent donor and may also allow conclusions on disease progress, severity, specific immune reaction and status.
However, working with antigen- and virus-specific T cells poses several challenges to researchers. Their low frequencies often hamper a reliable analysis. Specificity, inflammatory environment, subtype as well as detection limit and background are determining factors and thus require optimized procedures in order to facilitate a successful experiment. Moreover, potentially hazardous material poses a high risk of infection to the operator.
In response, researchers are exploring more reliable and safe workflow solutions for efficient stimulation, precise analysis as well as safe and gentle cell sorting in especially the context of infectious diseases such as COVID-19.
Miltenyi Biotec hereby offers a complete workflow addressing said challenges, with the SARS-CoV-2 PepTivator® Peptide Pools, REAfinity™ Recombinant Antibodies and flow analysis kits as well as closed and aerosol-free cell sorting on the MACSQuant® Tyto®.
It's all about finding the needle in the haystack!

Presentation by Outstanding Young Immunology Researcher Award Winners
「若手免疫学研究支援事業受賞者成果発表」

Elucidation of surface marker profiles defining progenitor exhausted T cells

○Yuki Kagoya
Division of Immune Response, Aichi Cancer Center Research Institute / Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, USA.

Exhausted T cells comprise a heterogeneous population, in which only less differentiated T cells called progenitor exhausted T cells (T_{PEX}) can be reinvigorated by immune checkpoint blockade. In this study, we thoroughly explored surface marker profiles that are able to define T_{PEX} using an *in vivo* adoptive cancer immunotherapy model. I will present our screening experiment results and discuss functional roles of a candidate molecule in antitumor T cells.

Differentiation of a novel memory-phenotype $CD4^+$ T lymphocyte population and its immunological significance

○Takeshi Kawabe
Department of Microbiology and Immunology, Tohoku University Graduate School of Medicine, Sendai, Japan / Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, USA

We recently reported that $CD4^+$ T lymphocytes contain an innate memory-phenotype (MP) cell population in steady state. However, it is unclear whether MP cells are heterogeneous, and if so, what signals specify their differentiation. Here we show that among MP cells, T-bet^{hi} subset is the population with innate immune function and generated dependently of DC1-derived IL-12. In the presentation we will discuss the detailed mechanism of this tonic IL-12 production as well as further characterization of MP cells.

In vivo spatial transcriptomics reveals the effect of anti-PD-L1 treatment in the supply of tumor-infiltrating CD8$^+$ T cells in Lewis lung carcinoma model in mice.

○Shigeyuki Shichino, Satoshi Ueha, Chang-Yu Chen, and Kouji Matsushima
Tokyo University of Science, Japan

Immune-checkpoint blockades (ICB) exert anti-tumor effect by activating CD8$^+$ T cells. However, which supply of CD8$^+$ T cell subsets are affected by ICB remains elusive. To address this question, we analyzed LLC tumor by combining intravenous staining (IVS) and scRNA-seq. We found that anti-PD-L1 treatment decreased the frequency of stem-like CD8$^+$ T cells and, increased terminally-exhausted/ proliferated CD8$^+$ T cells. We also found that anti-PD-L1 treatment only increased the frequency of 24hrs IVS$^+$ exhaust progenitor-2 (Gzma^{hi} Nr4a1^{hi} Ccr2^{hi} Rora^{hi}), suggesting that anti-PD-L1 might enhance supply of exhaust progenitor-2 from blood circulation, and local proliferation of terminally-exhausted CD8$^+$ T cells. These results may point out the action of anti-PD-L1 therapy in the supply of tumor-infiltrating CD8$^+$ T cells.

Clinical Seminar 1

Immunogenicity of biologic therapies in immune-mediated diseases

○Keishi Fujio
The University of Tokyo

In recent years, the use of antibodies and other biologics has become widespread in a variety of diseases. Biologics have a clear mode of action which is associated with few side effects. However, their foreign epitopes sometimes induce the immune response, which can be problematic in reducing their effectiveness. Clinical data from a number of drugs, including anti-TNF inhibitor antibodies, have shown that antidrug antibodies can attenuate the efficacy of treatment and prevent continuation of treatment. Although the appearance of antibodies can be suppressed by immunosuppression, there are some cases in which immunosuppression cannot be used due to patient complications. IL-6 receptor-inhibiting antibodies are less frequent than TNF-inhibiting antibiotic antibodies, which may be influenced by the class of biologic agents. Therefore, less immunogenic preparations are being developed, and recently approved drugs tend to be less immunogenic than existing drugs. This seminar will discuss the immunogenicity of biologics and the treatment of immune-mediated diseases in light of the latest reports.

Clinical Seminar 2

Multiple mechanisms of action of abatacept in treatment of rheumatoid arthritis

○Masataka Kuwana
Nippon Medical School Graduate School of Medicine, Tokyo, Japan

Rheumatoid arthritis (RA) is one of systemic autoimmune diseases that mainly affects joint synovium. More than 80% of the patients have circulating autoantibodies, such as rheumatoid factor and anti-citrullinated antigen antibodies (ACPA), which are shown to be pathogenic. In fact, rituximab and abatacept, CTLA4-Ig, are effective for RA. The mechanism of action of abatacept is believed to be competitive inhibition of T-cell co-stimulation mediated through binding of CD28 to CD80/CD86 on antigen-presenting cells, resulting in induction of anergy in antigen-exposed T cells. On the other hand, recent studies suggest that signal transduction through binding of abatacept to CD80/CD86 on monocyte-lineage cells is potentially involved in the therapeutic action of abatacept. Namely, abatacept directly suppresses differentiation of osteoclast precursors within circulating monocytes through upregulation of Indolamine 2,3-dioxygenase (IDO), leading to inhibition of formation of bone erosions. We have recently found direct effects of abatacept on circulating monocytes, which down-regulate expression of CD64 and inhibit ACPA-immune complex-mediated inflammatory cytokine production. Abatacept has a unique mechanism of action that suppresses pathogenic processes of RA in multiple checkpoints.

Clinical Seminar 3

Treatment of rheumatoid arthritis under COVID19 pandemic - Mechanisms and related immunosuppressive therapy

○Isao Matsumoto
Division of Rheumatology, Department of Internal Medicine, University of Tsukuba

The COVID-19 pandemic has significantly changed the landscape of healthcare. Some patients with rheumatoid arthritis (RA) are concerned that RA may make them susceptible to severe forms of infection, or avoid visiting crowded hospitals where possible, and/or wish to minimize immunosuppressive therapy. On the other hand, dramatic advances in the management of RA are ongoing, and the earliest possible diagnosis and active intervention are recommended, with the goal of inducing and maintaining remission even in patients with high disease activity. Currently, many types of drugs, such as TNF inhibitors, IL-6 inhibitors, selective T-cell costimulation blockers, and JAK inhibitors, are available in Japan, but there remains a gap between remission induction and maintenance; in real-world settings, some patients achieve resolution of inflammation but still experience subjective symptoms such as stiffness and pain, which fail to improve adequately.

JAK inhibitors, which are as effective as biologics, are currently approved in five drug products. JAK inhibitors are small-molecule compounds that inhibit the activity of kinase functioning downstream of cytokine receptors and have a variety of targets. Their availability in oral forms offers great advantages, including improved treatment compliance.

This seminar discusses and provides an overview of the importance of remission maintenance and its association with immunosuppressive therapy in the management of RA amid the coronavirus pandemic, with some insights into new pathogenetic mechanisms of RA and characteristics of JAK inhibitors.

Clinical Seminar 4

Recent developments in eosinophilic granulomatosis with polyangiitis

○Shunsuke Furuta
Chiba University

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare form of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides characterized by small vessel vasculitis associated with bronchial asthma and eosinophilia. This presentation will focus on recent developments in EGPA. As to the criteria for EGPA, the new classification criteria for EGPA was generated by a large international cohort and will be launched in the near future. The new criteria are expected to have better sensitivity and specificity than the previous ones.

In contrast to other forms of ANCA-associated vasculitis, roles of ANCA in EGPA are still largely unknown. There are phenotypic differences between ANCA-positive and -negative EGPA. A recent genome-wide association study revealed that there were two genetically distinct subgroups of EGPA, which correspond to ANCA-positive and -negative subgroups. Reliable evidence of treatment for EGPA is still limited at the moment. Thus, there are no strong recommendations for treatment of EGPA. Recently the efficacy of mepolizumab, anti-IL-5 antibody, for EGPA were proved by a randomized controlled trial. Currently, various new drugs are under evaluation.

Clinical Seminar 5

COVID-19 virological understanding and treatment / prevention strategy

○Kimiyasu Shiraki
Senri Kinran University

Favipiravir has been developed as an anti-influenza drug and showed a broad spectrum of anti-RNA virus activity. The mode of antiviral action is a chain terminator of RNA strand elongation at the incorporated site similar to acyclovir in herpes virus and favipiravir shows the therapeutic efficacy in lethal RNA virus infection with high viral load by reducing viral replication. Plasma level of favipiravir in influenza dose far exceeded the antiviral concentration of favipiravir against SARS-CoV-2 and favipiravir demonstrating clinical efficacy in clinical trials in COVID-19 patients. COVID-19 pneumonia is a 3-week illness consisting of a viral growth period and an inflammatory reaction time due to an immune response and Favipiravir significantly reduced the time to clinical improvement in patients with COVID-19 pneumonia from 14.7 days to 11.9 days in the placebo group. This indicated that favipiravir reduced viral growth time by 2.8 days and inhibited 11 viral replication cycles, because the antiviral drug cannot shorten the time of immune response and inflammation.

Clinical Seminar 6

Recent advances and challenges with immune checkpoint inhibitors

○Shohei Koyama
Division of Cancer Immunology, Research Institute/Exploratory Oncology Research & Clinical Trial Center (EPOC), National Cancer Center / Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine

Immune checkpoint inhibitors (ICIs) have been approved for multiple types of cancers. A long-term durable response is a feature of this treatment; however, only some patients have favorable response to ICIs. To improve outcomes, mechanisms underlying either sensitivity or resistance to ICIs need to be elucidated. In this seminar, I will talk about recent advances and challenges with ICIs from immunologic and genetic perspectives.

Clinical Seminar 7

Reconsidering IL-6 receptor inhibition in autoimmune and inflammatory conditions

○Isao Matsumoto
Division of Rheumatology, Department of Internal Medicine, University of Tsukuba

Recent therapies for rheumatoid arthritis (RA) are dramatically progressed continuously, and a lot of biologics targeting inflammatory cytokines (TNF alpha and IL-6), T cells-co stimulator and JAK are available in Japan. From the view of the effective therapy with new molecular, immunological and genetic studies, the etiology of RA has been reconsidered. Especially, IL-6 blockade has been approved for the treatment of RA, juvenile idiopathic arthritis, adult-onset Still's disease, giant cell arteritis and Takayasu arteritis, neuromyelitis optica, Castleman disease and cytokine release syndrome. As well known, IL-6 is proinflammatory cytokine that has multiple roles in the dysfunction of the immune and inflammatory systems. In this seminar, we will discuss about the evidence of anti-IL-6R therapy in bone destruction and skeletal muscle. Also, we will discuss about the mechanisms of autoimmune arthritis mainly focusing on another acute phase protein, such as inter-alpha-trypsin inhibitor heavy chain4 (ITIH4),that is proved major increased protein in post RA progression with native and its citrullinated form.

Clinical Seminar 8

Advance in synovial biology and blockade of TNFα-induced signaling pathways

○Shinsuke Yasuda
Tokyo Medical and Dental University

In patients with rheumatoid arthritis (RA), fibroblast-like synoviocytes (FLS) play essential roles such as pannus formation, invasion and release of several key molecules including IL-6, RANKL and MMPs. Recently, multi-omics studies on RA-synovium revealed signal pathways relevant to RA, FLS subsets related to RA which produce inflammatory cytokines and the existence of FLS-like cells in peripheral blood from pre-flare patients. Nevertheless, TNFα-induced behavioral changes in FLS substantially contribute to the pathophysiology of RA. Under continuous stimulation of TNFα, RA-FLS turns to inflammatory/proliferative phenotype, mainly via activation of NF-kB and MAP kinase pathways. Recently we identified that NF-kB, generally recognized as the downstream of RANKL-RANK, binds to the promoter of RANKL and induce its expression. Such positive feedback loop would be a realistic treatment target for RA. microRNA-9 accelerated degradation of NF-kB1 and reduced RANKL expression in RA-FLS. Intra-articular microRNA-9 administration ameliorated collagen-induced arthritis in rats. RasGRP1,3 and 4 activates Ras upstream of MAP kinase pathway, while RasGRP2 activates Rap1 inducing actin aggregation and NF-kB pathway activation. We identified high expression of RasGRP2/4 in a subset of RA patients. Intra-articular knockdown of RasGRP2/4 also ameliorates collagen-induced arthritis. In clinical practice, TNF-inhibitor with low immunogenicity exerts long-standing efficacy in the majority of TA patients. Thus, as treatment strategies for RA, TNFα-induced signal pathway could be currently inhibited by anti-TNFα monoclonal antibodies, and would be abrogated at multiple steps in near future, hopefully.

Clinical Seminar 9

Recent advancement in immune-mediated neuropathies

○Sonoko Misawa
Department of Neurology, Graduate School of Medicine, Chiba University

There are numbers of immune mediated disorders that affect the central and peripheral nervous systems. This walk will introduce recent advancement in pathophysiology, diagnosis, and treatment of Guiilain Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) that are representative immune mediated peripheral nervous disorders.

GBS typically causes acute tetraplegia after preceding infection. Almost 20% of patients cannot walk independently even after one year from the onset if they are treated appropriately by immunoglobulin of plasma pheresis. There can be numbers of pathological pathways during acute phase of GBS. Among them, activation of complement and resulting membrane attack complex formation can be the final step leading to irreversible nerve damage. Novel drugs, such as monoclonal antibody that targets complement protein and IgG degrading enzyme of Streptococcus pyogenes, have been applied to GBS.

CIDP is a demyelinating polyneuropathy that causes chronic progressive weakness and paresthesia. CIDP has been considered as a syndrome that consists of multiple disorders, because there are different clinical phenotypes regarding symptoms, courses, and treatment responsiveness. New pathogenic autoantibodies, such as NF155 and CNTN1 antibodies, were found and clinical phenotypes of CIDP related those antibodies have been demonstrated. They are usually refractory to standard care such as steroid, immunoglobuline, and plasmapheresis, and rituximab has been applied to treat them.

Clinical Seminar 10

Recent advances in understanding the JAK-related pathogenesis of rheumatoid arthritis.

○Hirofumi Shoda
Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo

Several cytokines contribute to the pathogenesis of rheumatoid arthritis (RA), and biological reagents against inflammatory cytokines, such as TNF-alpha and IL-6, occupy the main position in the therapeutic strategy of RA. Recently, JAK inhibitors are also regarded as indispensable drugs for the treatment of RA. Many clinical studies demonstrated the efficacy of JAK inhibitors and long term observation revealed their safety profiles.

Recent advances in the basic studies shed light on the new players in the pathogenesis of RA. Particularly, multi-omics study focuses on the synovial infiltrated cells. One of the important players is peripheral helper T (Tph) cells. Tph cells infiltrate RA synovial tissue and help B cell accumulation and differentiation. Tph cells induce antibody secretion from B cells via IL-21. IL-21 signaling depends on JAK1/3. Indeed, there are some reports, which showed that tofacitinib has an impact on B cells.

Another important player is fibroblast-like synoviocytes (FLS). Recent studies showed that CD90+FLS has a pro-inflammatory phenotype and is a key player in the pathogenesis of RA. Our recent study revealed that cytokine combination is required for epigenetic changes and the transcription of inflammatory genes in FLS (Tsuchiya H, Ohta M, et al. Ann Rheu Dis. accepted).

In this session, recent advances in understanding the JAK-related pathogenesis of RA will be reviewed and discussed together.

Clinical Seminar 11

The current trend of Progressive-Fibrosing Interstitial Lung Disease (PF-ILD)

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PF-ILD is a collective term used for indications that share a common progressive phenotype. The phenotype is characterized by worsening respiratory symptoms, lung function decline, limited response to immune-modulatory therapies, decreased quality of life, and potentially, early death. Interstitial lung disease (ILD) encompasses a large group of more than 200 parenchymal pulmonary disorders, of which the majority are classified as rare. ILD is further classifies into various types and subtypes. The major classification includes idiopathic interstitial pneumonia (IIPs) including idiopathic pulmonary fibrosis (IPF), autoimmune ILDs, hypersensitivity pneumonitis (HP), sarcoidosis, and several other ILDs. Further, IIPs are classified into idiopathic pulmonary fibrosis (IPF), iNSIP, unclassifiable IIPs, and others IIPs. Autoimmune ILDs are classified into interstitial pneumonia with autoimmune features (IPAF), RA-ILD, SSc-ILD, and other autoimmune ILDs.
Evidence-based treatment for patients with PF-ILD are currently limited, and often receive corticosteroids. Because of commonalities between IPF and PF-ILDs, it has been proposed that the potential efficacy and tolerability of antifibrotic drugs, like nintedanib, should be evaluated in PF-ILDs. By far, the most commonly used first-line therapy for all the non-IPF fibrosing ILDs was corticosteroids. Because PF-ILDs have been defined by fibrotic progression despite conventional therapy, there is inherently a substantial unmet need for the treatment of these conditions. Antifibrotic drugs effective to slow down disease progression in IPF may conceivably have comparable efficacy in other PF-ILDs.