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23–25 November 2018

Tokyo, Japan

"Future direction of research and treatment of intractable diseases (Nanbyo)" & "Interdisciplinary approach to osteoarticular pathology and Bio-Rheumatology"

WILEY

International Journal of Rheumatic Diseases

Tokyo Moscow International Medical Forum 2018 (TOMO Forum 2018)
Toward Medical Excellence in Eurasia
23-25 November 2018
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Contents

Conference Outline

Tokyo-Moscow International Medical Forum 2018 (TOMO2018)

Organizers

- Japan Medical Research Foundation (JMRF)
- National Graduate Institute for Policy Studies (GRIPS)
- Moscow State University of Medicine and Dentistry (MSUMD)
- Russian Foundation for Basic Research (RFBR)

Co-Chairmen of the Joint Organizing Committee

Kusuki Nishioka

Chairman of the Board of Directors, Japan Medical Research Foundation (JMRF)

Senior Fellow, National Graduate Institute for Policy Studies (GRIPS)

Oleg Yanushevich

Rector, Moscow State University of Medicine and Dentistry (MSUMD)

Corresponding member of the Russian Academy of Sciences (RAS)

Supporters

<Japan>

- Ministry of Foreign Affairs (MOFA)
- Ministry of Education, Culture, Sports, Science and Technology (MEXT)
- Ministry of Health, Labour and Welfare (MHLW)
- Ministry of Economy, Trade and Industry (METI)
- Japan Business Federation (KEIDANREN)
- Japan Pharmaceutical Manufacturers Association (JPMA)
- Japan Rheumatism Foundation (JRF)
- Japanese Orthopaedic Association (JOA)
- Japanese Association of Rehabilitation Medicine (JARM)

<Russian Federation>

- Ministry of Foreign Affairs of the Russian Federation
- Ministry of Health of the Russian Federation
- Ministry of Science and Higher Education of the Russian Federation
- Embassy of the Russian Federation in Japan
- Russian Medical Society

Duration

Friday, 23rd November – Sunday, 25th November, 2018

Conference Theme

Future direction of global health care program
“Future direction of research and treatment of intractable diseases (Nanbyo)” &“Interdisciplinary approach to osteoarticular pathology and Bio-Rheumatology”

Venue

National Graduate Institute for Policy Studies (GRIPS)
7-22-1 Roppongi Minato-ku, Tokyo, Japan 106-8677
http://www.grips.ac.jp/en/

November 23 (Friday)

Innovation of Global Care

Room 1 (Soukairou Hall)

9:00 - 9:20

Opening Ceremony

Opening Addresses

Kusuki Nishioka (Japan)
Co-Chairman of the Organizing Committee
Japan Medical Research Foundation (JMRF), Japan
National Graduate Institute for Policy Studies（GRIPS), Japan

Oleg Yanushevich (Russia)
Co-Chairman of the Organizing Committee
Russian Academy of Sciences, Russia
Moscow State University of Medicine and Dentistry (MSUMD), Russia

Vladislav Panchenko (Russia)
Member of the Organizing Committee
Chairman of the Board of Directors,Russian Foundation for Basic Research

Mikhail Galuzin (Russia)
Ambassador Extraordinary and Plenipotentiary of the Russian Federation to Japan

Norio Mitsuya (Japan)
House of Representatives, Japan

Messages

Minister of Foreign Affairs, Japan
Minister of Health, Labour and Welfare, Japan
Minister of Health, Russian Federation
President of Japan Rheumatism Foundation

9:20 - 10:00

Opening Lecture

Chairs :

Kusuki Nishioka (Japan)
Japan Medical Research Foundation (JMRF), Japan
National Graduate Institute for Policy Studies（GRIPS), Japan

Oleg Yanushevich (Russia)
Moscow State University of Medicine and Dentistry (MSUMD), Russia
Corresponding member of the Russian Academy of Sciences (RAS), Russia

Challenges of Biomedical Research in Uncertain World

Kiyoshi Kurokawa (Japan)
The University of Tokyo, Japan
National Graduate Institute for Policy Studies (GRIPS), Japan

10:00 - 11:00

RS-1 Towards the Dissemination of the Advanced Medical Therapy in Russia

Chairs :

Kusuki Nishioka (Japan)
Japan Medical Research Foundation (JMRF), Japan
National Graduate Institute for Policy Studies (GRIPS), Japan

Igor Maev (Russia)
Moscow State University of Medicine and Dentistry (MSUMD), Russia
Academician of the Russian Academy of Sciences (RAS), Russia

RS-1-1 Medical Education in Russia

Oleg Yanushevich (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

Corresponding member of the Russian Academy of Sciences (RAS), Russia

RS-1-2 Screening Technologies to Study Biodiversity

Alexander Gabibov (Russia)

Shemyakin & Ovchinnikov Institute of Bioorganic Chemistry, Russia

Laboratory of Biocatalysis Russian Academy of Sciences, Russia

11:00 - 12:00

JS-1 Future Prospects of Medical Policy in Japan

Chairs :

Masato Mugitani (Japan)

Tokyo Medical University, Japan

Alexander Gabibov (Russia)

M.M. Shemyakin and Yu.A. Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences (RAS), Russia

RFBR Board Member Academician of the Russian Academy of Sciences (RAS), Russia

JS-1-1 Current Status of and Challenges in Addressing Intractable/Rare Diseases in Japan

Takahiro Kawano (Japan)

Ministry of Health, Labour and Welfare, Japan

JS-1-2 Healthcare Innovation in Super-Aged Society

Kazumi Nishikawa (Japan)

Ministry of Economy, Trade and Industry, Japan

10 minutes break

12:10 - 13:10

LS-1 Keynote Luncheon Lecture

Chair : Evgeny Zhilyaev (Russia)

European Medical Center, Russia

Russian Medical Academy of Continuing Professional Education, Russia

Total Management Care System Program for Patients of Rheumatic Disorders and Associated Disorders Throughout: Performance of Over 30-Year Activities in Japan Rheumatism Foundation

Kusuki Nishioka (Japan)

Japan Medical Research Foundation (JMRF), Japan

National Graduate Institute for Policy Studies（GRIPS), Japan

10 minutes break

13:20 - 14:10

RS-2 Recent Progress of Immunology in Russia

Chairs :

Ko Okumura (Japan)

Atopy/Allergy Research Center, Juntendo University Graduate School of Medicine, Japan

Igor Malyshev (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

Ilya Metchnikoff and Paul Ehrlich - 1908 Nobel Prize Winners for Their Research “Theory of Immunity”

Valery Chereshnev (Russia)

Russian Society of Immunology, Russia

Member of Rusian Academy of Sciences (RAS), Russia

14:10 - 15:15

JS-2-1 Current and Future Prospect of Epoch-Making Cure Medicine for Intractable Diseases, Introduced by Anti-IL- 6 Receptor Antibody (1)

Chairs :

Kiyoshi Kurokawa (Japan)

The University of Tokyo, Japan

National Graduate Institute for Policy Studies (GRIPS), Japan

Kusuki Nishioka (Japan)

Japan Medical Research Foundation (JMRF), Japan

National Graduate Institute for Policy Studies (GRIPS), Japan

Sponsored by Chugai Pharmaceutical Co., Ltd.,

JS-2-1-1 From the Discovery of IL-6 and the Development of Anti-IL-6R Anti Body

Tadamitsu Kishimoto (Japan)

Immunology Frontier Research Center, Osaka University, Japan

JS-2-1-2 Innovative Development of Anti-Interleukin-6 Receptor Antibody in the Treatment of Intractable Immune-Inflammatory Diseases: Current Status and Future Prospects

Norihiro Nishimoto (Japan)

Tokyo Medical University, Japan

Osaka Rheumatology Clinic, Japan

Coffee break (15minutes)

15:30 - 16:00

JS-2-2 Current and Future Prospect of Epoch-Making Cure Medicine for Intractable Diseases, Introduced by Anti-IL- 6 Receptor Antibody (2)

Chairs :

Kiyoshi Kurokawa (Japan)

The University of Tokyo, Japan

National Graduate Institute for Policy Studies (GRIPS), Japan

Kusuki Nishioka (Japan)

Japan Medical Research Foundation (JMRF), Japan

National Graduate Institute for Policy Studies (GRIPS), Japan

Sponsored by Chugai Pharmaceutical Co., Ltd.,

How Innovative Antibody Engineering Technologies are Expanding the World of Antibody Drugs

Junichi Nezu (Japan)

Chugai Pharmaceutical Co., Ltd., Japan

16:00 - 16:50

RS-3 Current Situation and Perspective for Treatment of Intractable Diseases in Russia

Chairs :

Kusuki Nishioka (Japan)

Japan Medical Research Foundation (JMRF), Japan

National Graduate Institute for Policy Studies (GRIPS), Japan

Valery Chereshnev (Russia)

Russian Society of Immunology, Russia

Member of Russian Academy of Sciences(RAS), Russia

RS-3-1 The Gut Microbiome in Crohn's Disease

Igor Maev (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

Academician of the Russian Academy of Sciences (RAS), Russia

RS-3-2 Progressive Course of Liver Fibrosis in Patients Coinfected with HIV and HCV from the Point of View of Rational Antiviral Therapy

Irina Balmasova (Russia)
Laboratory of pathogenesis and treatments for infectious diseases of Research Institute of Medicine and Dentistry, Russia

10 minutes break

17:00 - 18:00

JS-3 Development of Novel Drugs and Medicare Cost

Chair : Kazumi Nishikawa (Japan)
Ministry of Economy, Trade and Industry, Japan

Sponsored by AYUMI Pharmaceutical Corporation

The Series of Developing New Bio-Chemicals and Medical Expenditure in Japan

Masato Mugitani (Japan)
Tokyo Medical University, Japan

November 23 (Friday)

Innovation of Global Care

Room 2 (Meeting Room 1A, 1B, 1C)

15:30 - 16:30

RS-6-1 Session for Young Researchers (1)

Chairs :

Nobuyuki Udagawa (Japan)
Matsumoto Dental University, Japan

Dmitry Lezhnev (Russia)
Moscow State University of Medicine and Dentistry (MSUMD), Russia

RS-6-1-1 Health Impacts of Bike Sharing System in Moscow

Irina Bakalova (Belgium/Russia)
KU Leuven, Belgium
Research Institution Higher School of Economics, Russia

RS-6-1-2 Virtual Reality Balance Training in Parkinson`s Disease Patients with Movements Recording Devices

Ekaterina Kamenskikh (Russia)
Siberian State Medical University, Russia

RS-6-1-3 Predictors of Discontinuation for Target Treatment for Rheumatoid Arthritis Due to Adverse Events

Ekaterina Koltsova (Russia)
Moscow Clinical Scientific Center, Russia
Research Institute of the Organization of health and healthcare management, Russia

RS-6-1-4 Lactate: Not Only a Key Metabolite, But a Regulator of Antigen-Antibody Interaction

Valeriya Kuzmicheva (Russia)
Samara State Medical University, Russia

RS-6-1-5 High Level of Systemic Inflammation in HIV/Hepatitis C Coinfection is Linked to Hepatocellular Injury

Evgeniia Saidakova (Russia)
Institution of Ecology and Genetics of Microorganisms,
Russian Academy of Sciences, Russia

RS-6-1-6 Asphyxia in Newborns: Comparison of Different Methods of Therapeutic Hypothermia

Dmitrii Spiridonov (Russia)
Pirogov Russian National Research Medical University, Russia

10 minutes break

16:40 - 17:40

RS-6-2 Session for Young Researchers (2)

Chairs :

Yoko Ishihara (Japan)

Japan Medical Research Foundation, Japan

Svetlana Lyamina (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

RS-6-2-1 Cervical Insufficiency: Diagnosis and Management

M.M. Astrakhantseva (Russia)

Pirogov Russian National Research Medical University, Russia

Centre for Family Planning and Reproduction, Russia

RS-6-2-2 The Variant Anatomy of Nasal Bones and Pyriform Apertures Using Multislice Computed Tomography

Margarita Dutova (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

RS-6-2-3 Aspects of the Current of Oral Lichen Planus in the Identification of Human Papillomavirus Infection

Viktoriia Starshinina (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

RS-6-2-4 M3 Macrophages Stop Division of Tumor Cells Received from Human Prostate Tumor Bioptate in vitro

Sergei Kalish (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

RS-6-2-5 Effect of Immediate Alveolar Ridge Preservation After Tooth Extraction

Nikolay Redko (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

RS-6-2-6 Association of Cytokine Profile with Endothelial Dysfunction and 24-Hours Blood Pressure in Patients with Exacerbation of Chronic Obstructive Pulmonary Disease

Natalia Smetneva (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

November 24 (Saturday)

General Theme: Next-Generation Treatment of Intractable Diseases
-Bio-Medicine and Therapeutic Vaccines-

Room 1 (Soukairou Hall)

9:00 - 10:20

JS-4-1 Post-Bio Strategies (1)

Chairs :

Tetsuya Tomita (Japan)

Osaka University Graduate School of Medicine, Japan

Igor Malyshev (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

JS-4-1-1 The Whole Picture of New Bio Treatment: Coming Era of Therapeutic Vaccine

Kusuki Nishioka (Japan)

Japan Medical Research Foundation (JMRF), Japan

National Graduate Institute for Policy Studies (GRIPS), Japan

JS-4-1-2 DNA Vaccination for the Treatment of Adult Common Disease

Ryuichi Morishita (Japan)

Osaka University Graduate School of Medicine, Japan

Headquarter for The Healthcare Policy, Japan

5 minutes break

10:25 - 11:55

JS-4-2 Post-Bio Strategies (2)

Chairs :

Kusuki Nishioka (Japan)

Japan Medical Research Foundation (JMRF), Japan

National Graduate Institute for Policy Studies（GRIPS), Japan

Andrey Pikhlak (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

JS-4-2-1 Vaccinating Against Cytokines to Treat Inflammatory Diseases

Marie-Christophe Boissier (France)

University Paris 13, France

JS-4-2-2 DNA Vaccines for the Treatment of Allergy

Shigetada Furukawa (Japan)

Astellas Pharma Inc., Japan

10 minutes break

12:05 - 13:05

LS-2 Luncheon Seminar 2

New Frontier in Therapeutic Innovation for Rare Diseases

Chairs :

Yuji Sato (Japan)

JCR Pharmaceuticals, Japan

Yoshikatsu Eto (Japan)

Advanced Clinical Research Center, Institute of Neurological Diseases, Japan

Tokyo Jikei University School of Medicine, Japan

Sponsored by JCR Pharmaceuticals Co., Ltd.

LS-2-1 Overview of Lysosomal Storage Disorders (LSD) : Recent Advances of the Treatment

Yoshikatsu Eto (Japan)

Advanced Clinical Research Center, Institute of Neurological Diseases, Japan

Tokyo Jikei University School of Medicine, Japan

LS-2-2 New Drug Development in Rare Diseases: Evolution, Challenges and Paths Forward

Yuji Sato (Japan)

JCR Pharmaceuticals, Japan

10 minutes break

13:15 - 14:05

RS-4 New Opportunities for Medical Technology from Decoding Inflammatory Resolution Mechanisms

Chairs :

Kusuki Nishioka (Japan)

Japan Medical Research Foundation (JMRF), Japan

National Graduate Institute for Policy Studies（GRIPS), Japan

Valery Chereshnev (Russia)

Russian Society of Immunology, Russia

Member of Russian Academy of Sciences (RAS), Russia

RS-4-1 Macrophage and Lymphocyte Reprogramming in vitro for Correction of an Disturbed Immune Response in vivo

Igor Malyshev (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

RS-4-2 Biotherapy of Gout Inflammation: Past and Future

Andrey Pikhlak (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

RS-4-3 Gout Simulation in vivo and in vitro: The Key Points

Svetlana Lyamina (Russia)

Moscow State University of Medicine and Dentistry, Moscow, Russia

14:05 - 15:05

JS-5 Bio-Medicine for Dermatological Diseases

Chair : Hidehisa Saeki (Japan)

Nippon Medical School, Japan

Sponsored by Janssen Pharmaceutical K.K.

Recent Advances in Psoriasis Therapy

Hitoshi Mizutani (Japan)

Mie University Graduate school of Medicine, Japan

15:05 - 16:05

JS-6 Bio-Medicine for Bone and Joint Diseases

Chair : Naoto Tamura (Japan)

Juntendo University Faculty of Medicine, Japan

Sponsored by Mitsubishi Tanabe Pharma Corporation

Current Anti-TNF Therapy and the Therapeutic Potential of the IL-17A Vaccine in Ankylosing Spondylitis

Tetsuya Tomita (Japan)

Osaka University Graduate School of Medicine, Japan

Coffee break (10minutes)

16:15 - 17:15

JS-7 Bio-Medicine for Gastrointestinal Diseases

Chair : Tadakazu Hisamatsu (Japan)

Kyorin University School of Medicine, Japan

Sponsored by Mitsubishi Tanabe Pharma Corporation

Optimal Use of Biologics in Inflammatory Bowel Disease

Masayuki Saruta (Japan)

The Jikei University School of Medicine, Japan

17:15 - 18:15

JS-8 Bio-Medicine for Cranial Nerve Diseases

Chair : Kusuki Nishioka (Japan)

Japan Medical Research Foundation (JMRF), Japan

National Graduate Institute for Policy Studies (GRIPS), Japan

Sponsored by Eisai Co., Ltd.

Potential Immunotherapies for Parkinson's Disease as a Protein Conformation Disorder

Nobutaka Hattori (Japan)

Juntendo University, Japan

10 minutes break

18:25 - 19:25

ES-1 **Evening Seminar**

Development of Fully Human Anti-IL-6 Receptor Monoclonal Antibody, and their Clinical Potential

Chair : Hisashi Yamanaka (Japan)

Tokyo Women's Medical University, Japan

Sponsored by Asahi Kasei Pharma Corporation

The Diagnosis and Treatment of Rheumatoid Arthritis
- A Discussion on the Clinical Potential of a Fully-Human Anti-IL-6R Monoclonal Antibody (Sarilumab)

Mitsumasa Kishimoto (Japan)

Immuno-Rheumatology Center, St. Luke's International Hospital, Japan

November 24 (Saturday)

Next-Generation Treatment of Intractable Diseases
-Bio-medicine and Therapeutic Vaccines-

Room 2 (Meeting Room 1A, 1B, 1C)

12:05 - 13:05

LS-3 **Luncheon Seminar 3**

Chair : Akio Morinobu (Japan)

Kobe University Graduate School of Medicine, Japan

Sponsored by ONO PHARMACEUTICAL CO., LTD./Bristol-Myers Squibb K.K.

Education Program of Rheumatology in Japan, EU & US and Safety Use of Biologics in Training Hospital

Masato Okada (Japan)

Immuno-Rheumatology Center, St. Luke's International University Hospital, Japan

10 minutes break

13:15 - 15:15

GS-1 **Paradime Change for a Rehabilitation Program**

Chairs :

Masahiko Mukaino (Japan)

Fujita Health University, Japan

Alexander Epifanov (Russia)

Moscow State University of Medicine and Dentistry (MSUMD), Russia

GS-1-1 **Cybernic Treatment Using the Cyborg-Type Robot Hybrid Assistive Limb Enhanced Functional Regeneration in Patients with Rare Incurable Neuromuscular Diseases (Nanbyo)**

Takashi Nakajima (Japan)

Niigata National Hospital, National Hospital Organization, Japan

GS-1-2 **Diagnostic Functional Statement of Dental System**

Evgeny Solovykh (Russia)

Federal state autonomous educational institution of higher education
I.M.Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation, Russia

GS-1-3 Innovations in Measurement Technologies in the Field of Rehabilitation Medicine

Masahiko Mukaino (Japan)
Fujita Health University, Japan

10 minutes break

15:25 - 16:15

RS-5-1 Frontier Science in Russia (1)

Chairs :

Mitsumasa Kishimoto (Japan)
Immuno-Rheumatology Center, St. Luke's International Hospital, Japan
Evgeny Zhilyaev (Russia)
European Medical Center, Russia
Russian Medical Academy of Continuing Professional Education, Russia

RS-5-1-1 Clinical and Epidemiological Differences of Chronic Non-Bacterial Osteomyelitis in Russian Federation

Mikhail Kostik (Russia)
Saint-Petersburg State Pediatric Medical University, Russia

RS-5-1-2 Surgical Procedure in Diagnosis and Treatment of Spinal Form of Non-Bacterial Osteomyelitis in Children

Alexander Mushkin (Russia)
Federal State Budget Institute "Science research Institute of Phthisiopulmonology", Russia

Coffee break (10minutes)

16:25 - 17:40

RS-5-2 Frontier Science in Russia (2)
- Metal intolerance. Mechanisms, identification and manifestations -

Chairs :

Mitsumasa Kishimoto (Japan)
Immuno-Rheumatology Center, St. Luke's International Hospital, Japan
Evgeny Zhilyaev (Russia)
European Medical Center, Russia
Russian Medical Academy of Continuing Professional Education, Russia

RS-5-2-1 Protein Allergy and Metal Allergy. The Evolution of Autoimmunity Concept in Immunology

Mark Goloviznin (Russia)
Moscow State University of Medicine and Dentistry (MSUMD), Russia

RS-5-2-2 Local and Systemic Mechanisms of Hypersensitivity to Alloys of Dissimilar Metals

Ulyana Pikhlak (Russia)
Research Institute of Medicine and Dentistry, Russia

RS-5-2-3 Human Mineral and Trace Element Status: Personalized and Population-Based Approaches

Andrei Grabeklis (Russia)
RUDN University, Russia
Russian Society for Trace Elements in Medicine, Russia

November 25 (Sunday)

Next-Generation Treatment of Intractable Diseases
-From the Perspective of Global Care-

Room 1 (Soukairou Hall)

9:00 - 12:00

GS-2 Bio-Medicine Viewed from Global Healthcare Perspective: Problems to be Solved

Chairs :

Mark Goloviznin (Russia)

Moscow State University of Medicine and Dentistry(MSUMD), Russia

Nan Shen (China)

Shanghai Jiao Tong University School of Medicine, China

GS-2-1 Personalization of Targeted Treatment for Rheumatoid Arthritis

Evgeny Zhilyaev (Russia)

European Medical Center, Russia

Russian Medical Academy of Continuing Professional Education, Russia

GS-2-2 Current Situation of Rheumatic Disease Treatment in Mongolia

Zulgerel Dandii (Mongolia)

Mongolian National University of Medical Sciences (MNUMS) , Mongolia

GS-2-3 Features of Joint Syndrome and Treatment Specifics in the Population of Tajikistan

Surayo Shukurova (Tajikistan)

Postgraduate Health Education Institute, Tajikistan

GS-2-4 Clinical Features of SAPHO Syndrome

Yoko Ishihara (Japan)

Japan Medical Research Foundation, Japan

GS-2-5 New Insights into the Pathogenesis of Systemic Lupus Erythematosus: Finding Novel Players and Therapeutic Targets

Nan Shen (China)

Shanghai JiaoTong University School of Medicine, China

10 minutes break

12:10 - 13:10

LS-4 Luncheon Seminar 4

Chair : Kusuki Nishioka (Japan)

Japan Medical Research Foundation (JMRF), Japan

National Graduate Institute for Policy Studies (GRIPS), Japan

Sponsored by Eisai Co., Ltd.

Clinical Research of Fibromyalgia in Japan

Chie Usui (Japan)

Juntendo University Faculty of Medicine, Japan

10 minutes break

13:20 - 14:40

JS-9 Creation of Highly Advanced Medical Drugs and the Way for Reduction of Medical Expenses

Chairs : Masato Mugitani (Japan)

Tokyo Medical University, Japan

Kusuki Nishioka (Japan)

Japan Medical Research Foundation (JMRF), Japan

National Graduate Institute for Policy Studies (GRIPS), Japan

Sponsored by AYUMI Pharmaceutical Corporation/Kyowa Hakko Kirin Co., Ltd.

JS-9-1 The Working Life of the Elderly and a Sustainable Social Security System

Jiro Kawasaki (Japan)

House of Representatives, Japan

JS-9-2 Toward Bringing Innovation in Drug Discovery to the World

Yoshihiko Hatanaka (Japan)

Japan Pharmaceutical Manufacturers Association (JPMA), Japan

Astellas Pharma Inc., Japan

14:40 - 15:00

Closing Ceremony

DOI: 10.1111/1756-185X.13534

OPENING LECTURE

WILEY International Journal of Rheumatic Diseases

Challenges of biomedical research in uncertain world

K. Kurokawa[1,2]

[1]The University of Tokyo, Japan; [2]National Graduate Institute for Policy Studies (GRIPS), Japan

We have achieved fantastic progresses over last 100+ years overcoming many medical challenges, primarily infectious diseases through 1970s, then cancer and life-style-related diseases such as hypertension, diabetes, atherosclerosis, obesity and amazing longevity to "Life Shift" living through 100 years. The progress owes largely to science & technologies motivated by many medical doctors and scientists facing many human sufferings, ie, patients, that led to innovative diagnostic and invasive technologies, drugs. Fruits of progresses are now associated often with soaring healthcare cost, ie, pressing the issue who pays for the cost. As we live longer and enjoy longevity, we now face the consequences of aging brain, dementia, which has become a major challenges of our time. On the other hands, digital-technology-driven rapidly advancing "globalization" brought social and world affairs somewhat uncertain and unstable, which underlie dysfunctional conventional democracy, changes in social and paradigm with widening income disparity, dividing further those who "Have" and "Not Have". Where advances in digital and biomedical technologies may lead us? This will be the topic of my presentation.

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RS-1-1 | Medical education in Russia

O. Yanushevich[1,2]

[1]Moscow State University of Medicine and Dentistry (MSUMD), Russia;
[2]Corresponding member of the Russian Academy of Sciences (RAS), Russia

The history of the development and formation of medical education in Russia is 260 years old. It all started with the opening of the Faculty of Medicine at Moscow University in 1758. The main asset of medical education at all times is the practical preparation and training of students at the university clinic. Medical education in the USSR has reached a new level of quality of training, one of the important principles, the organization of the health care system and a wide coverage of the population, while maintaining the best traditions of the russian medical school. Modern medical education in Russia has absorbed the best traditions of previous medical schools and is developing in accordance with the requirements of the new time. The main is the technological transformation of the science and practice of modern medicine. As well as the level of practical training of doctors. Today, medical education is carried out by 46 medical universities and 36 medical faculties in classical universities. 245.000 students study there.
Features of medical education in Russia:

- a large amount of training hours for practical training in the clinic;
- medical practice of students as medical orderlies and numbers;
- the formation of an educational program based on the professional standard;
- accreditation of medical graduates.

RS-1-2 | Screening technologies to study biodiversity

A. Gabibov[1,2]

[1]Shemyakin & Ovchinnikov Institute of Bioorganic Chemistry, Russia;
[2]Laboratory of Biocatalysis Russian Academy of Sciences, Russia

Combinatorial chemistry and biology became a hallmark of life science in XXI century. We developed microfluidic approaches for screening microbiota, biocatalytic clones, antibody diversity and specific chimeric antigen receptors (CARs). We report the development of a novel platform to significantly enhance the efficacy and safety of Follicular lymphoma treatment. Combinatorial autocrine-based selection is used to rapidly identify specific ligands for these B cell receptors on the surface of FL tumor cells. The selected ligands are used in a CAR-T format for redirection of human CTLs. Essentially, the format is the inverse of the usual CAR-T protocol. Ultrahigh-throughput screening techniques can identify unique functionality from millions of variants. To mimic the natural selection mechanisms that occur by compartmentalization in vivo, we developed a technique based on single-cell encapsulation in droplets of a monodisperse microfluidic double water-in-oil-in-water emulsion. The combination of droplet-generating machinery with FACS followed by next-generation sequencing and liquid chromatography-mass spectrometry analysis of the secretomes of encapsulated organisms yielded detailed genotype/phenotype descriptions. This platform was probed with uHTS for biocatalysts anchored to yeast with enrichment close to the theoretically calculated limit and cell-to-cell interactions. The versatility of the platform allowed the identification of bacteria, including slow-growing oral microbiota species that suppress the growth of a common pathogen. We developed a novel platform for maturation of antibody molecule in silica. In vitro selection of antibodies from large repertoires of immunoglobulin (Ig) combining sites using combinatorial libraries is a powerful tool, with great potential for generating in vivo scavengers for toxins. We approached this goal using quantum mechanics/molecular mechanics (QM/MM) calculations to achieve maturation in silico.

JS-1-1 | Current status of and challenges in addressing intractable/rare diseases in Japan

T. Kawano

Intractable/Rare Diseases Control Division, Health Service Bureau, Ministry of Health, Labour and Welfare, Japan

Measures to address intractable/rare diseases in Japan were initiated based on cases of subacute myelo-optico-neuropathy (SMON) in 1972. Since then, such measures have been implemented under the Act on Medical Care for Patients with Intractable/Rare Diseases (hereinafter referred to as the Act on Intractable/Rare Diseases), the current version of which was enforced on January 1, 2015, after several revisions. Under the Act on Intractable/Rare Diseases, intractable/rare diseases are defined as rare diseases of unclear pathogenic mechanism, for which the treatment methods have not been established and which require affected patients to undergo long-term medical treatment.
Under the current Act on Intractable/Rare Diseases, the measures to address intractable/rare diseases have been changed from the traditional research-oriented approach into a comprehensive program that also covers welfare aspects. Under this act, measures focusing on the following three objectives are to be implemented.

1. Development of effective treatment methods and improvement in the quality of medical care.
2. Construction of a fair and stable system for supporting health care costs.
3. Enhancement of the public's understanding of the diseases and expansion of measures to encourage patients' social participation.

Since enforcement of the current Act on Intractable/Rare Diseases, measures to address intractable/rare diseases have been expanding; however, the coverage of health care costs has also expanded to include 331 diseases. In the future, therefore, additional measures to address intractable/rare diseases will be required to advance research, establish a health care service system for early diagnosis, and reinforce the support system by which patients with intractable/rare diseases can gain and maintain employment that can accommodate their condition.

JS-1-2 | Healthcare innovation in super-aged society

K. Nishikawa

Healthcare Industries Division, Ministry of Economy, Trade and Industry, Japan

This session will discuss the roles of innovation (business and technology innovations) in developing a society where people can produce, consume, and actively work for a living, regardless of their age, in Japan, the first country to experience a super-aged society.

The topics include the importance of managing age-related and lifestyle-related diseases in addition to the traditional medical approaches, the importance of involving a wide range of industries that have been less relevant to healthcare, and the importance of applying technology, such as digital technology. These topics will be covered presenting some examples in the management of dementia and diabetes. In addition, the importance of the coordination between services that are covered or not covered by public health insurance will be discussed.

Furthermore, an introduction to the need to globally disseminate Japanese innovations at various occasions, such as the Well Ageing Society Summit, which will be held in October in Japan, will be provided.

LS-1 | Total management care system program for patients of rheumatic disorders and associated disorders throughout: performance of over 30-year activities in Japan rheumatism foundation

K. Nishioka[1,2]

[1]*Japan Medical Research Foundation(JMRF), Japan;* [2]*National Graduate Institute for Policy Studies (GRIPS), Japan*

Among symptoms of Rheumatoid arthritis, rheumatism and other autoimmune collagen disease, there are many symptoms of intractable diseases that straddle multiple areas of other clinical departments, not only department of orthopaedics, but also the departments of dermatology, respiratory and neurology, cardiology, pediatrics, gastroenterology, and the mental care.

However, patients are receiving diagnosis by single clinical department, even in general hospitals, and in most cases, they are not getting proper diagnosis treatment by specialized medical doctors. In addition, even if patients are receiving diagnostic examinations of plural clinical departments, information are not shared by departments concerned, thus each departmental diagnostic treatment result are not utilized and reflected in actual treatment of patients.

Japanese Ministry of Health, Labor and Welfare has successfully established epoch making system through Regional Comprehensive Care Project, to offer meticulous treatment for rheumatoid arthritis disease and other incurable diseases, especially bio-treatment for patients anywhere in Japan.

Furthermore, in order to cope with Japan's aging society, system is also being developed currently not only for physicians in local regional communities, but also for case-workers and various medical personnel including nurses, pharmacists, physical therapists, occupational therapists.

In this session, we want to raise the issues about the total care system in the treatment of rheumatic diseases and other incurable diseases.

RS-2 | Ilya Metchnikoff and Paul Ehrlich—1908 Nobel Prize winners for their research "Theory of Immunity"

V. A. Chereshnev[1,2]; M. V. Chereshneva[1,2]; A. Yu. Gavrilova[1,2]

[1]*Russian Society of Immunology, Russia;* [2]*Member of Russian Academy of Sciences (RAS), Russia*

The aims of the work are the historical reconstruction of the key events of the immunology genesis and development and the evaluation of scientific, methodological and social role of Ilya Metchnikoff and Paul Ehrlich in the development of this field if science as an independent discipline.

The work is devoted to the 110th anniversary of the award of Ilya Metchnikoff and Paul Ehrlich for their research on immunity with a Nobel Prize. Therefore, in the framework of the work, the characteristics of the world immunology development, the chronicle of the priority discoveries and the influence on the development of immunology of these two eminent scientists are discussed. The scientific biographies of Ilya Metchnikoff and Paul Ehrlich were studied based on the concepts of socio-psychological characteristics of the creative personality formation and the substantive aspect of scientific activity within the inner logic of scientific ideas development. Ilya Metchnikoff and Paul Ehrlich contributions in

the creation of cellular and humoral theories of immunity, which for many years were accompanied by hot polemics, until the Nobel Prize in 1908 has brought the official line under this discussion, are described.

That is why the specific aspects of scientific discussions of immunology of the late XIX—early XX centuries with the detailed analysis of their origin is presented in the study. The activities of individual scientists, international and national research centers of applied and theoretical immunology have been also analyzed in the work. The results of analysis revealed the importance of not only scientific, but also the social factors in the development of immunology.

JS-2-1-1 | From the discovery of IL-6 and the development of anti-IL-6R anti body

T. Kishimoto

Immunology Frontier Research Center, Osaka University, Japan

A series of our studies in IL-6 have revealed that it has a pleiotropic activity in various tissues and cells and its deregulated expression is responsible for several chronic inflammations and hemopoietic malignancies. Humanized antibody against 80kd IL-6R (Tocilizumab) has shown therapeutic effect in RA, JIA, Castleman's diseases and LVV. Recently, TH17 is shown to be responsible for the pathogenesis of autoimmune diseases and IL-6 together with TGF-β are essential for the induction of TH17. We identified a new transcription factor required for Th17 cell induction. This molecule, aryl hydrocarbon receptor (Ahr) interacts with Stat1 and Stat5 and abrogate their negative activity in the induction of Th17 cell differentiation. Experimental arthritis is completely abrogated in T cell-specific Ahr-deficient mice. Therapeutic effect of Tocilizumab confirmed that over and constitutive-production of IL-6 is responsible for the pathogenesis of autoimmune diseases. Then, the question to be asked is how is IL-6 production regulated. We identified a novel molecule called Arid5a which binds with the 3′- UTR of IL-6 mRNA and protects its degradation by competing with Regnase-1.Interestingly, this molecule is present in nuclei and inflammatory stimulation induced translocation of Arid5a from nuclei into cytoplasm and it competes with Regnase-1 for the protection of mRNA of IL-6. Arid5a binds with the 3′-UTR of not only IL-6mRNA but also STAT3 mRNA in TH17 cells as well as T-bet mRNA in TH1 cells. Thus, Arid5a accelerates Th17cell differentiation in inflammation as well as exacerbation of IFN-γ-mediated septic shock. All these results indicate that Arid5a is one of the key molecules for inflammation as well as the development of septic shock. The results also suggest the therapeutic potential of antiagonistic agents for Arid5a in the prevention of various incurable inflammatory diseases and septic shock.

JS-2-1-2 | Innovative development of anti-interleukin-6 receptor antibody in the treatment of intractable immune-inflammatory diseases: current status and future prospects

N. Nishimoto[1,2]

[1]*Department of Molecular Regulation for Intractable Diseases, Institute of Medical Science, Tokyo Medical University, Japan;* [2]*Osaka Rheumatology Clinic, Japan*

Interleukin-6 (IL-6) is a multifunctional cytokine that regulates immune reactions, inflammation and hematopoiesis. Although IL-6 plays important physiological roles, deregulated overproduction of IL-6 causes various clinical symptoms such as fever, fatigue, and wasting symptoms, and laboratory abnormalities including leukocytosis, hyper-γ-globulinemia, emergence of autoantibodies, and increase in serum acute phase proteins. Furthermore, IL-6 is pathologically involved in the various immune-inflammatory diseases such as rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). Thus, IL-6 can be a good target for the treatment of these diseases. Tocilizumab (TCZ), a humanized anti-IL-6 receptor antibody, was designed as a therapeutic agent to inhibit specifically IL-6 signaling. TCZ was developed in Japan and is the first IL-6 inhibitor that has been approved in clinical use in the world, while various therapeutic antibodies targeting IL-6 have been currently developed.

A series of clinical studies have shown the efficacy and safety of TCZ in patients with Castleman disease, RA, JIA, giant cell arteritis (GCA) and Takayasu arteritis who are refractory to conventional therapies including corticosteroids. The successful clinical development of TCZ confirmed the pathological significance of IL-6 in such diseases. IL-6 inhibition is now considered as a therapy for numerous diseases. In the forum, current status and future prospects of IL-6 inhibition therapy in intractable immune-inflammatory diseases will be discussed.

JS-2-2 | How innovative antibody engineering technologies are expanding the world of antibody drugs

J. Nezu

Research Division, Chugai Pharmaceutical Co., Ltd., Japan

The ability to humanize an antibody molecule obtained from an immunized animal opened the door for antibody drugs as a promising therapeutic modality. Since beginning in the 1990's, the world of antibody drugs has grown very rapidly, and many successful ones are used to treat patients for whom there are no other therapeutic options. One such drug is an anti-IL-6R antibody called Actemra, the first antibody drug to be created by Japanese pharma. The antibody drug world continues to grow, powered by the development of new technology in antibody engineering. At Chugai Pharmaceutical, we have developed a series of antibody

engineering technologies. One of these is Recycling antibody™ technology, which is achieved by engineering the binding domain of an antibody molecule to give it a pH-dependent antigen-binding property. Because this property reduces the antigen-mediated clearance of the antibody, the serum half-life of a Recycling antibody is prolonged. An advanced version of Recycling antibody is Sweeping antibody™, which can accelerate the clearance of a soluble antigen from plasma due to its pH-dependent binding property and enhanced binding of Fc to the Fc receptor. Another way that antibody engineering provides many possibilities for antibody drug discovery is by creating a bispecific antibody. Hemlibra™ is a bispecific antibody drug recently developed by Chugai and approved for treating patients with hemophilia A. This talk will discuss further applications for bispecific antibody technology and look at how these new antibody engineering technologies will change the world of antibody drugs in future.

RS-3-1 | The gut microbiome in Crohn's disease

I. Maev[1,2]; D. Andreev[1,2]; V. Govorun[1,2]

[1]*Moscow State University of Medicine and Dentistry (MSUMD), Russia;* [2]*Academician of the Russian Academy of Sciences (RAS), Russia*

Background: Crohn's disease (CD) is a chronic generalized inflammation of the gastrointestinal tract. Many factors, both genetic and environmental, are regarded to contribute to the CD pathogenesis. It is a general notion that CD is a result of abnormal immune response of genetically susceptible individuals to the imbalance in the intestinal microbiota. Among dysbiosis in CD patients 10-100 fold increase in abundance of Escherichia coli is often observed as compared to healthy individuals, so this led to several studies of *E. coli* isolated from those patients.

Materials: We performed the shotgun genome sequencing of 28 *E. coli* isolates from ten CD patients and compared genomes from these isolates with already published genomes of CD strains and other pathogenic and non-pathogenic strains.

Results: The plasmid and several operons from the reference CD-associated *E. coli* (CDEC) strain LF82 were demonstrated to be more often present in CDEC genomes belonging to different phylogenetic groups than in genomes of commensal strains. The operons include carbon-source induced invasion GimA island, prophage I, iron uptake operons I and II, capsular assembly pathogenetic island IV and propanediol and galactitol utilization operons.

Conclusions: Our findings suggest that CDEC are phylogenetically diverse. Though no CD-specific genes or functional domains were present in all CD-associated strains, some genes and operons are more often found in the genomes of CDEC than in commensal *E. coli*. They are principally linked to gut colonization and utilization of propanediol and other sugar alcohols.

RS-3-2 | Progressive course of liver fibrosis in patients coinfected with HIV/HCV from the point of view of rational antiviral therapy

N. D. Yushchuk[1,2]; I. P. Balmasova[3,4]

[1]*Full Member of Russian Academy of Sciences (RAS), Russia;* [2]*Moscow State University of Medicine and Dentistry (MSUMD), Russia;* [3]*A.I. Yevdokimov Moscow State University of Medicine and Dentistry, Russia;* [4]*Laboratory of pathogenesis and treatments for infectious diseases of Research Institute of Medicine and Dentistry, Russia*

The aim of the study was to determine the effect of the order of HIV and HCV admission to coinfected patient on the course of the liver fibrosis and the effectiveness of antiviral therapy. The objectives of the study included the identification of the relationship between the order of the pathogens entry and the viral load of HIV and HCV, the frequency of the progressive course of liver fibrosis, the influence of different groups of antiretroviral and anti-HCV drugs on the progression of the fibrous process. It was found that when HIV is the first pathogen, the viral load of HIV is lower and HCV is higher than when the first pathogen is presented by HCV. HIV as the first pathogen twice as often contributes to the development of progressive course of liver fibrosis. HCV as the first pathogen causes an increase in the frequency of progressive liver fibrosis if only HIV reverse transcriptase inhibitors are used for antiretroviral therapy and pegylated interferon alpha and ribavirin are used for anti-HCV therapy. In combination therapy, the most successful combination is antiretroviral therapy with the inclusion of protease or integrase inhibitors, if HCV is the first pathogen. The same combination is less effective if the first pathogen is HIV. The results show the clinical significance of determining the order of HIV and HCV infection in predicting the risk of progressive course of liver fibrosis and the appointment of antiviral therapy.

JS-3 | The series of developing new bio-chemicals and medical expenditure in Japan

M. Mugitani

Tokyo Medical University, Japan

Many patients, inter alia, fallen Rheumatoid arthritis, have taken advantageous benefits by availability of new bio-chemicals at these days, in terms of their quality of daily life. Since these bio-chemicals have developed based on molecule-targeting therapeutic agent, they have come in the market one after another within these ten years surprisingly faster than the traditional chemical compound development.

REMICAD (Infliximab) initiated such new therapeutic movement and has followed by ENBREL (Etanercept), ACTEMRA (Tocilizumab), HUMIRA (Adalimumab), SINMPONI (Golimumab), etc.

These new medicines have brought a tremendous effect against several diseases such as Rheumatoid arthritis, while we have faced another issue concerning medical expenditure in terms of both a

personal payment at a medical facility and a total cost of national health insurance.

As Pharmaceutical enterprises spent a lot of investment in order to develop such molecule-targeting therapeutic agents, the retail price were recognized very expensive relatively. In view of this, national health insurance should absorb a large amount of payment for those new medicines.

That is an issue. I would like to analyze concerned elements for the recent situation and to propose several optimal options on the table.

RS-6-1-1 | Health impacts of bike sharing system in Moscow

I. Bakalova[1,2]

[1]KU Leuven, Belgium; [2]Research Institution Higher School of Economics, Russia

Physical inactivity is a major cause of many health problems of urban population. Creating conditions for active lifestyle has become an important challenge for urban planners, one of solutions may be a city bike-sharing program.

In 2013 in Moscow was launched a bike-sharing system Velobike. The purpose of this study is to analyze the impact of Velobike on public health. I use yearly individual data from the Russia Longitudinal Monitoring Survey of HSE, from 2012 to 2016. I focus on adults from 20 to 50 years old, excluding disabled, overall 3,390 observations. In the figure below we can see how the behavior of respondents is affected by the introduction of Velobike. We may see that the share of bike users in Moscow has increased with the development of Velobike. Then I estimate logit model in Python to see how bike usage affects the probability of having health issues. As explanatory variables I use age, gender, marital status, monthly income, education, eat habits, smoker/non-smoker and bicycle usage. I show that the probability of suffering from obesity decreases by 4.5% if a respondent uses a bicycle, significance at 0.09 level. I also show that the probability of assessing overall health condition as «Bad» is by 4.2% lower for cyclists, significance at 0.03 level.

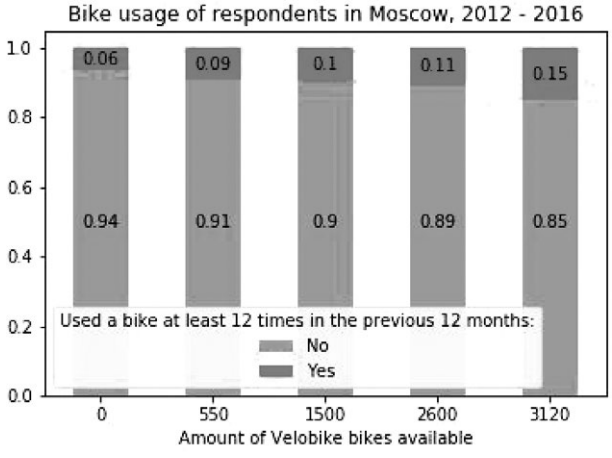


Figure 1: Share of respondents who used a bike has increased with the development of Velobike infrastructure.

Based on the presented results I reckon that introduction of Velobike system promotes cycling to Moscow inhabitants, which has a positive effect on people's health.

RS-6-1-2 | Virtual reality balance training in Parkinson's disease patients with movements recording devices

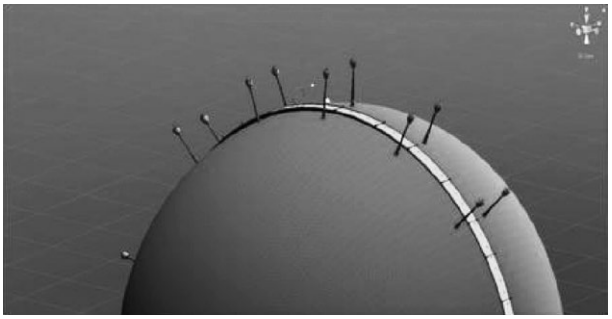
E. M. Kamenskikh; I. V. Tolmachev; I. A. Zhukova

Department of Neurology and Neurosurgery, Siberian State Medical University, Russia

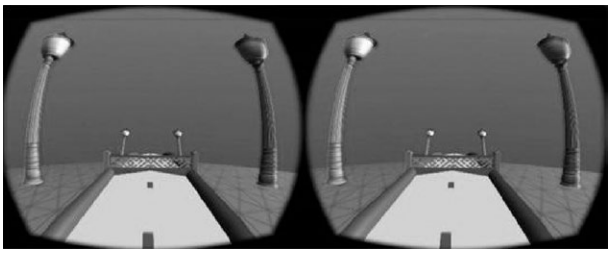
Aim: To design the method of treating balance dysfunction in patients with Parkinson's disease (PD) using Virtual reality (VR).

Tasks:

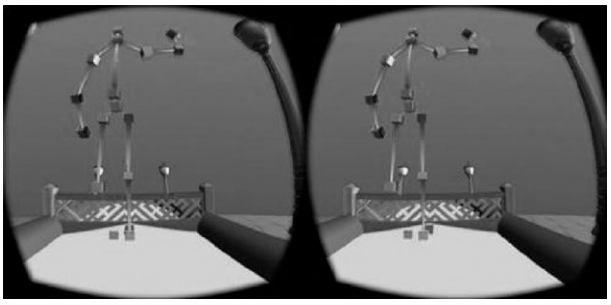
1. To create a moving virtual reality scene "The round Earth";



2. To add visual impetus in the VR scene;
3. To connect the VR scene with Microsoft (MS) Kinect and VR glasses Epson;

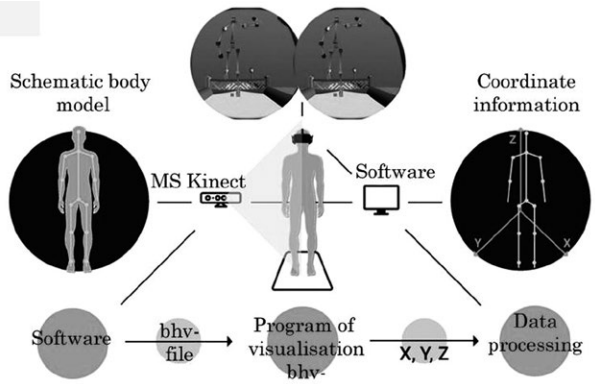


4. To add biofeedback using data from the MS Kinect;



5. To make some adjustments to the scene after the participation of a small group of patients in the study.

Results: A small group of patients with PD participated in the research. They needed to put on VR glasses, stay for 15 seconds in Romberg position and then walk for 45 seconds and return to Romberg position for 15 seconds.



Conclusion:

1. Participating in this research patients didn`t suffer any injuries or traumas;
2. As a visual impetus we used small fences, which patients needed to bypass by changing height and length of steps, paying attention to special features of PD motor deficit;
3. For the first time as biofeedback at first time we used a group of main points of the body, which had been recorded by MS Kinect. But then it was changed for a schematic model, because it was more understandable for elderly patients;
4. The next aim of the research is to enlarge a group of patients and create a control group for searching differences between them, using a coordinate data from MS Kinect.

RS-6-1-3 | Predictors of discontinuation for target treatment for rheumatoid arthritis due to adverse events

E. N. Koltsova[1,2]; G. V. Lukina[1]; E. I. Schmidt[3]; E. V. Zhilyaev[4,5]

[1]Moscow Clinical Scientific Center Moscow, Russia; [2]Research Institute of the Organization of health and healthcare management, Moscow, Russia; [3]City Clinical Hospital 1 named after N.I. Pirogov, Moscow, Russia; [4]Russian Medical Academy of continuing professional education, Moscow, Russia; [5]CJSC «European Medical Center», Moscow, Russia

The aim: To detect predictors of target drug withdrawal due to adverse events among patients with rheumatoid arthritis.

Materials and methods: The study includes patients with rheumatoid arthritis from the Moscow Arthritis Registry (MAR), receiving treatment with biologics or tofacitinib. Search for predictors was carried out in two steps. At the first step we selected variables which demonstrated significant correlation with time to treatment discontinuation in Kaplan-Meier analysis. At the second step selected factors were included in the Cox regression model. The final set of independent significant predictors was obtained by backward stepwise variable selection.

Results: Analysis includes 1,230 treatment events in 696 patients. The mean age was 57.1 years. The mean observation time—5.3 years. There were 146 cases of therapy discontinuation due to adverse events. Presence of rheumatoid nodules ($P < 0.001$), higher doses of glucocorticoids ($P < 0.001$), lower doses of methotrexate ($P = 0.009$) were independent significant predictors of increased risk of treatment withdrawal. Used target drug also showed independent significant correlation with this risk. Relative risk (compared to Etanercept) was for Infliximab = 6.57(CI: 3.69-11.73), Certolizumab—2.61 (CI: 1.23-5.56), Abatacept—1.23 (CI: 0.65-2.30), Adalimumab—1.37 (CI: 0.75-2.50), Rituximab—0.56 (CI: 0.26-1.20), Tofacitinib—0.46 (CI: 0.15-1.40), Tocilizumab—0.77 (CI: 0.37-1.60).

Conclusion: The use of sufficient doses of methotrexate, a reduction in use of glucocorticoids can be considered as a measure to prevent adverse events when using target drugs. There are significant differences between target drugs for the risk of cancellation due to adverse events.

RS-6-1-4 | Lactate: not only a key metabolite, but a regulator of antigen-antibody interaction

V. Kuzmicheva

Department of Fundamental and Clinical Biochemistry and Laboratory Diagnostics, Samara State Medical University, Russia

Through much of the history lactic acid has been wrong considered as a waste product of glycolysis. Last years a more beneficial side of lactate as a regulator of energy metabolism, immune tolerance, memory formation and cancer growth has been demonstrated. However, we still lack knowledge revealing the mechanisms of lactate-to-inner cell structures interactions.

The main purpose of this work is to study how lactate influences immune reactions using the example of antigen-antibody interaction. Our objectives are to predict potential biological effects of lactate using programs for computer modeling PASS and STITCH, to create an experimental system based on the ABO blood groups antigens to test the most important effects in terms of immune reactions, to visualize the interaction between lactate and antigen-antibody complexes using confocal microscopy.

The findings of the research illustrate that according to PASS and STITCH prediction lactate has over 500 biological effects. Introduction of lactate in physiological concentration into the antigen-antibody system causes a number of conformational modifications in antigen determinants revealed in changes in time of the onset of agglutination and its degree. Antigens A and B show different stability while interacting with lactate, what was well registered on microphotographs obtained using confocal microscopy.

Our data provide key arguments supporting the idea that lactate is not only an energy source for different tissues but also an important regulator of multiple cell processes including immune reactions. Further research and a better understanding of lactate role in human organism will impact medical practice and benefit treatment approaches to the patients with various immune pathology.

RS-6-1-5 | High level of systemic inflammation in HIV/hepatitis C coinfection is linked to hepatocellular injury

E. V. Saidakova; K. V. Shmagel; L. B. Korolevskaya; N. G. Shmagel; V. A. Chereshnev

Laboratory of Ecological Immunology, Institute of Ecology and Genetics of Microorganisms, Ural Branch of the Russian Academy of Sciences, Russia

While chronic human immunodeficiency virus (HIV) infection and hepatitis C virus (HCV) infection are associated with the development of systemic inflammation, its level during HIV/HCV-coinfection is not well defined. We asked if treated HIV-monoinfected patients have different systemic inflammation level than HIV/HCV-coinfected subjects and if so, is it related to the hepatic damage indices.

In order to reach the purpose of the research we set several tasks. First was to collect blood samples from the well defined HIV-positive cohort in Perm, Russia. The work was done in compliance with all the requirements of the Institutional Review Board. Second task was to analyze some blood markers of systemic inflammation (IL-6, IP-10, sTNF-RI, and sTNF-RII). Third task was to estimate indices of monocyte/macrophage activation (sCD163, sCD14, and neopterin). Fourth task was to detect markers of intestinal epithelial barrier loss (I-FABP and LPS) and hepatic damage (AST, ALT, APRI). As a result we found that plasma levels of IL-6, IP-10, sCD163, and sTNF-RII were higher in HIV/HCV-coinfection than in HIV-monoinfection. HCV viral load was related to no inflammatory indices except for sCD163. Several markers (IP-10, neopterin, and sCD163) were positively correlated with the hepatic damage indices. Levels of I-FABP were comparably increased in both HIV-monoinfection and HIV/HCV-coinfection, but LPS concentrations were high only in HIV/HCV-coinfection suggesting impaired hepatic clearance of bacterial products.

The results obtained led to the conclusion that hepatocellular injury in HIV/HCV-coinfection is linked to elevated levels of certain inflammatory cytokines and an apparent failure to clear translocated microbial products. That can result in additional immune activation which burdens HIV-infection course.

RS-6-1-6 | Asphyxia in newborns: comparison of different methods of therapeutic hypothermia

D. Spiridonov; A. Kuzina

Pirogov Russian National Research Medical University, Moscow, Russia

Therapeutic hypothermia (TH) is used in infants with hypoxic-ischemic encephalopathy. Data on the TH results, within various treatment protocols, remain contradictory.

Thus the aim of the study was to compare the effectiveness of various methods of TH in complex therapy of post-hypoxic ischemic brain injury in newborns.

A retrospective analysis of 98 neonates with ante- or intranatal hypoxia was carried out: 46 (I group) undergone selective head cooling (SHC) with Olympic Cool-Cap® system; 25 (II group)—whole body cooling (WBC) with Arctic Sun® 5000 and 27 (III group)—CritiCool® system. Apgar score did not differ significantly in groups ($P > 0.05$). Inclusion criteria: gestational age ≥36 weeks, body weight >1,800 g, first 6 hours of life, an absence of intraventricular hemorrhage.

During first hours of life 83 (84.7%) newborns had seizures or increased seizure readiness ($P > 0.05$): 39 (84.8%), 20 (80.0%), 25 (92.6%), respectively. During TH seizures persisted in all neonates in group I (39%-100%), in groups II and III—14 (70.0%) and 14 (56.0%), respectively (I vs II, I vs III, $P < 0.05$). By the end of TH seizures were cured in 11 (28.2%), 16 (80.0%), 24 (96.0%) neonates, respectively (I vs II, I vs III $P < 0.05$). Prognosis concerning poor neurological outcomes was unfavorable in 23 (50.0%) newborns from SHC group. In WBC groups 19 (76.0%) and 27 (100%) neonates were discharged with favorable neurological dynamics.

WBC comparing with SHC is 2.8-3.4 times more effective and ensures a shorter period of positive neurological status dynamics achieving. In the CritiCool® group (III) there were no prognostic signs of cerebral palsy ($P < 0.05$).

RS-6-2-1 | Cervical insufficiency: diagnosis and management

M. M. Astrakhantseva[1,2]; G. M. Savelyeva[1,2]

[1]Obstetrics and gynecology department, Paediatric faculty, Pirogov Russian National Research Medical University, Moscow, Russia; [2]Obstetrics and gynecology department, Centre for Family Planning and Reproduction, Moscow, Russia

Objective: To improve diagnosis and management of cervical insufficiency (CI) in the second trimester of pregnancy.

Subject and methods: A prospective study (January 2015-October 2016) included 80 singleton pregnant women with cervical length ≤25 mm at 14-27 weeks of gestation. 73 patients were treated with vaginal cervical cerclage before 22 weeks of gestation—38/73 (52%), cervical pessary after 22 weeks of gestation—35/73 (48%). 50/73 (68.5%) received vaginal progesterone: 28/50 (56%)—with vaginal cervical cerclage, 22/50 (44%)—with cervical pessary.

Results: The treatment of CI appeared to be optimal in 69/73 (94.5%): 63/73 (86.3%) delivered at term and 6 (8.2%) delivered preterm—after 34 weeks. Totally 10/73 (13.7%) delivered preterm: 2—before 28 weeks, 2—between 28 and 32 weeks, 6—after 34 weeks. Preterm birth occurred in 5/38 (13.2%) patients with vaginal cervical cerclage: before and after 34 weeks in 2 and 3 patients, respectively (OR 0.67, 95% CI: 0.19-0.94). Among patients treated with cervical pessary 5/35 (14.3%) delivered preterm, 2—before 28 weeks, 3—after 34 weeks (OR 0.66, 95% CI: 0.014-1.23). Preterm birth occurred in 6/50 (12.0%) patients which were treated with vaginal progesterone combined with CI treatment: 3/28 (10.7%) patients with vaginal cervical cerclage and 3/22 (13.6%)—with cervical pessary (OR 0.68, 95% CI: 0.2-2.4).

Conclusions: Screening, diagnosis, and management of cervical insufficiency could be effective in 94.5% patients according to gestational age. Vaginal progesterone combined with cervical insufficiency treatment could be effective in 89.3% patients with vaginal cervical cerclage and in 86.4% patients with cervical pessary.

Key words: Cervical insufficiency, cervical length, vaginal cervical cerclage, cervical pessary, vaginal progesterone

RS-6-2-2 | The variant anatomy of nasal bones and pyriform apertures using multislice computed tomography

M. O. Dutova; D. A. Lezhnev; D. V. Davydov

Moscow State University of Medicine and Dentistry named after A.I. Evdokimov. Department of radiology, PhD student, Russia

Aims and objectives: To identify the anatomical variants of nasal bones and pyriform apertures in view of normal Caucasian and Asian (Mongoloid) configurations of external nose and different types of aesthetic nasal deformities using multislice computed tomography (MSCT, 64-slice).

Results: A total of nasal deformities (n = 132) were divided on the groups: rhinokyphosis (n = 36), long nose (n = 16), combined deformity like a hidden hump (n = 46), short nose (n = 16), wide nose (n = 17). The most frequent variants of pyriform apertures in patients group with normal Caucasian configuration (n = 43) of external nose are drop (39.5%) and heart (27.9%) types. The most common variants of nasal bones in all groups of these patients were II (40.1%), V (22.0%), VI (13.4%), VII (12.5%) types according to Lang and Baumeister. Every kind of deformities was described with their characteristic features of pyriform apertures and nasal bones. The generality of Asians (n = 24) has heart variant (87.5%) and VII (45.8%) type. Besides, the caudal part of nasal bones was also estimated due to variability of different marginal defects (symmetrical/asymmetrical, deep, unique) in the overwhelming amount of patients (78.4%). The Asians have mainly the smooth, symmetrical lacunae in 75.0% patients or whole nasal edge (20.8%).

Conclusion: MSCT permits to evaluate the different types of nasal deformities and to identify their anatomical base. The dominant variants of pyriform apertures are the drop and heart types as well as II, V, VI, VII forms of nasal bones. Every kind of deformities and ethnic specialties has their proper descripted variants of pyriform apertures and nasal bones with the statistically proved correlation between them ($P < 0.05$).

RS-6-2-3 | Aspects of the current of oral lichen planus in the identification of human papillomavirus infection

V. Starshinina

Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, department of Skin and veneral diseases, PhD student, Russia

Background: Oral lichen planus (OLP) is a chronic, long-term current disease with a variety of clinical manifestations, which are involved in the pathogenesis of immune, endocrine, intoxication, metabolic processes. Features of immune disorders in the OLP may lead to a 'supportive' environment for chronic human papilloma virus infection (HPV).

Aim: Explore the association between HPV and OLP.

Objectives:

1. To conduct polymerase chain reaction for detection of HPV;
2. To create 2 groups of research: one of this- patients with OLP and HPV, the second one- patients with only OLP;
3. To assess the severity of OLP in two groups;
4. To study the prevalence of clinical forms of both groups;
5. To study patient's hygienic status in two groups;
6. Identify the features of the disease OLP with HPV.

Results: HPV DNA of studied genotypes was detected in 53/58.8% cases. Atrophic/erythematous and erosive/ulcerative forms prevailed in this group, which was characterized by more severe course in 22/41.50% of patients with short periods of remission. Patients had significantly lower levels of oral hygiene in this group.

Conclusion: Features of OLP are found in identifying HPV: early onset; severe and frequent exacerbations of the disease, predominantly atrophic/erythematous and erosive/ulcerative forms.

RS-6-2-4 | M3 macrophages stop division of tumor cells received from human prostate tumor bioptate in vitro

S. Kalish

Department of Pathophysiology, Moscow State University of Medicine and Dentistry (MSUMD), Russia

Many tumors produce anti-inflammatory cytokines, which reprogram the anti-tumor M1 macrophages into the tumor-associated macrophages. We have hypothesized that the problem of pro-tumor macrophage reprogramming could be solved by using a special M3 switch phenotype. The M3 macrophages, in contrast to the M1 macrophages, should respond to anti-inflammatory cytokines by increasing production of pro-inflammatory cytokines to retain its anti-tumor properties.

Objective: Engineering of M3 switch phenotype in vitro and evaluation of M3 macrophage effect on growth rate of tumor cells isolated from human prostate tumor biopsy samples in vitro.

Methods: Macrophages of M1 and received after reprogramming M3 phenotype were incubated with tumor cells isolated from human prostate tumor biopsy samples. Reprogramming was represented on exposure to low doses of fetal bovine serum, Stat3/6 and Smad 3 transcription factor blockers, and lipopolysaccharide.

Results: The M3 switch phenotype can be designed by activation of M1-reprogramming pathways with simultaneous inhibition of the M2 phenotype(tumor associated) transcription factors, STAT3, STAT6, and/or SMAD3. M3 macrophages exerted an anti-tumor effect in vitro, which was superior to M1 macrophages. The anti-tumor effect of M3 macrophages was due to their anti-proliferative effect.

Conclusion: The observed significant inhibition of in vitro growth of tumor cells isolated from human prostate tumor biopsy samples by M3 macrophages give evidence of a clinical version of the suggested biotechnology for limitation of tumor growth by in vitro preprogrammed immune cells.

RS-6-2-5 | Effect of immediate alveolar ridge preservation after tooth extraction

N. Redko; A. Drobyshev

Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, department of maxillofacial and plastic surgery, Russia

Objectives: The most complete method of restoring the function of a lost tooth is dental implantation. The most difficulty in carrying out this manipulation is the insufficient amount of bone tissue after tooth extraction

The aim of our study is to analyze the effectiveness of using osteoplastic materials after tooth extraction for alveolar ridge preservation

Results: Eighty-four patients undergone tooth extraction. In 20 cases extraction socket was left untreated and allowed to heal under the blood clot, in 23 cases we made alveolar ridge preservation using natural bovine bone substitute (NBBS). Another 21 patients were treated by using autologous dentin matrix (ADM) of the extraction tooth. And the rest 20 cases we made with using plasma-rich growth factors (PRGF) for alveolar ridge preservation. After 12 ± 4 weeks an implantation was made. Also, trepan-biopsy was performed. Clinical and CBCT were made at day 0, 3 months, and 9 months postoperative. There were no large differences in general healing between the groups, however, the use of PRGF showed better soft-tissue healing in the early postoperative period. Comparison between groups showed a significant difference of bone resorption at 3 and 9 months. In the ARP groups (NBBS and ADM) was revealed significantly more trabecular bone formation. All dental implantations were successfully made in the follow-up period.

Conclusions: ARP via socket filling with a bone graft material can be an effective method to control bone resorption after tooth extraction, in both the horizontal and the vertical dimension.

RS-6-2-6 | Association of cytokine profile with endothelial dysfunction and 24-hours blood pressure in patients with exacerbation of chronic obstructive pulmonary disease

N. Smetneva

Moscow State University of Medicine and Dentistry, Faculty therapy and occupational diseases, Russia

Comorbidity of cardiovascular diseases and chronic obstructive pulmonary disease (COPD) represents an interdisciplinary problem. The chronic inflammation in the lung parenchyma is leading to cytokine imbalance not only in the lungs but also in the general circulation, leading to the development of systemic effects.

Purpose of the study: To study of the cytokine profile in blood serum and bronchoalveolar lavage in patients with exacerbation of COPD; to study of cytokine effect on 24-hours blood pressure (BP) and endothelial function.

Methods: 86 patients with COPD grade 2 group B (63.6 ± 10.5 years) and grade 3 group D (60.9 ± 2.64 years) GOLD in the acute phase and 32 healthy individuals in the control group (60 ± 2.62 years). We conducted: bronchological examination with bronchoalveolar lavage; determination of cytokines level in bronchoalveolar lavage and blood serum; 24-hour blood pressure monitoring on the brachial artery; asessement of endothelium-dependent vasodilatation of the brachial artery by the method of D.S. Celermajer.

Results: Patients with COPD had increased mean systolic and diastolic BP. There was a statistically significant reduction in the daily index in COPD grade 3 patients. The average daily BP in COPD 2 and 3 grades was associated by direct correlation with the concentration of pro-inflammatory cytokines IL-2 ($r = 0.79$, $P < 0.05$), IL-6 ($r = 0.83$, $P < 0.05$),IL-1β ($r = 0.93$, $P < 0.05$) and TNF-α ($r = 0.77$, $P < 0.05$) in the blood serum. The maximum diastolic BP in patients with COPD

2 and 3 grades was linked by a direct correlation with the concentration of pro-inflammatory cytokines IL-2 (r = 0.84, $P < 0.05$), IL-12r70 (r = 0.84, $P < 0.05$), INF-γ (r = 0.91, $P < 0.05$), TNF-α (r = 0.93, $P < 0.05$), TNF-β (r = 0.91, $P < 0.05$). Endothelial function also correlated with cytokine levels and worsened with grows of concentration of TNF-α (r = −0.77, $P < 0.05$), TNF-β (r = −0.72, $P < 0.05$), INF-γ (r = −0.74, $P < 0.05$).

Conclusion: The increase of pro-inflammatory cytokines concentrations in blood serum is associated both with grows of diastolic blood pressure meanings and with endothelial dysfunction. Identification of the markers of inflammation in COPD patients can reveal subjects in higher risk of general and cardiovascular complications, and lead to personilised therapeutic approaches.

JS-4-1-1 | The whole picture of new bio treatment: coming era of therapeutic vaccine

K. Nishioka[1,2]

[1]*Japan Medical Research Foundation (JMRF), Japan;* [2]*National Graduate Institute for Policy Studies (GRIPS), Japan*

The treatment of various rheumatic diseases such as Rheumatoid arthritis and other intractable diseases have made epoch-making progress, by the development of biological products.

Especially in rheumatoid arthritis, throughout changing a variety of treatment environment, with early diagnosis and treatment is made possible, and many patients are in remission stage. Thus, it is no exaggeration to say that rheumatoid arthritis is no longer considered as an "incurable" disease.

However, treatment with the drug formulation of biological products is expensive compared to previous compound drugs, and besides, frequent dosage is required at the start of administration, and therefore, clinical treatment is greatly influenced by the gap between rich and poor, and it is difficult to uphold the medical principle that everyone is entitled to receive equal treatment, which is frustrating in clinical practice.

In addition, there seems to be a similar trend of this current situation not only in Japan but also in the world, which must be considered to cope with in the future.

In order to counteract this situation, "therapeutic vaccine" will be considered as a treatment strategy for the next generation.

At the current stage, many of the therapeutic vaccines are still at the development stage, and they may be as high prices as biological products as well, but the treatment effect is considered much longer half-life than the biological product, if the design of adjuvant is effectively considered, and if its safety and evaluation is established, their efficacy is expected to continue probably for several years from the onset of the effect to over a lifetime. Thus would become potential epoch-making therapeutic strategies.

Considering these perspectives, we have conducted the simulation study with the hope to solve the current biological problems, so we report the study.

JS-4-1-2 | DNA vaccination for the treatment of adult common disease

R. Morishita[1,2]

[1]*Department of Clinical Gene Therapy, Osaka University Graduate School of Medicine, Japan;* [2]*Headquarter for Healthcare Policy (Chairman: Prime Minister Shinzo Abe), Japan*

Recently, we have focused on the therapeutic vaccination which has extended its scope from infectious diseases to chronic diseases, including cardiovascular diseases. We have reported that angiotensin II vaccine for hypertension or DPP4 vaccine for diabetes successfully attenuated high blood pressure or hyperglycemia in each mice model, respectively (PLoS One 2013, PNAS 2014, Sci Rep 2017, Stroke 2017). From the clinical point of view, to increase the efficacy of the drug adherence interventions may have a great impact on the health of the population, because it is reported that approximately 50% may not take medications among patients with chronic illness. This poor adherence to medication leads to increase the morbidity and mortality. If the improvement of drug compliance has been achieved with vaccines in hypertensive patients, it may assist the better control of blood pressure, leading to reduce the complications. As an initial challenge to confirm our working hypothesis, we have attempted to develop a therapeutic vaccine against hypertension. As a result, the vaccine-induced anti-angiotensin II antibodies can efficiently ameliorate angiotensin II-induced high blood pressure and perivascular fibrosis in mice. To prolong the vaccination, DNA vaccine might be more interesting. Now, our clinical trial of hypertension DNA vaccine has been started in Australia from 2018 as phase I/IIa. The potential of vaccine for hypertension offers an innovative treatment that could be very effective for the control of noncompliance which is one of the major problems in the management of hypertensive patients in the world. In this session, we would like to discuss about potential vaccination in terms of future medicine.

JS-4-2-1 | Vaccinating against cytokines to treat inflammatory diseases

M.-C. Boissier[1]; L. Semerano[1]; E. Assier[1]; P. Decker[1]; N. Bessis[1]; J.-F. Zagury[2]

[1]*Inserm U1125, Paris 13 University,Avicenne Hospital (APHP), Bobigny, France;* [2]*CNAM GBA, Paris, France*

Cytokine targeting proved effective for the treatment of several chronic inflammatory or autoimmune diseases, including rheumatoid arthritis (RA). Currently approved treatments in RA target inflammatory cytokines (like TNF-α, IL-1, IL-6, IL-12, IL-23) or their signaling intracellular pathways(kinase inhibitors). This represent passive

immunotherapy, most are monoclonal antibodies directed against the cytokine or its receptor. They revolutionized the treatment of inflammatory chronic diseases, despite inconstant and frequently incomplete effects which opens the way for novel strategies.

In this context, a novel type of anti-cytokine drugs based on vaccination is emerging. In this case, therapeutic antibodies are produced by the individual itself. This approach generates antibodies that are well-tolerated in the absence of allogenic or xenogenic epitopes.

The saga of anti-TNF-α vaccination recapitulates the different steps of such strategy. Several vaccination approaches were conducted in parallel to develop a vaccine against TNF-α. In order to induce a B cell response, DNA vaccination, introduction of a foreign Th cell epitope and coupling TNF-α (or peptides of TNF-α) with carrier proteins were developed in animal models of RA. Clinical trials were encouraging in early phase 2, but not confirmed in a larger trial in RA. Interestingly, anti-TNF vaccine was well tolerated, and experimental data confirmed its favourable risk/benefit ratio regarding infection susceptibility. Other cytokines such as IL-1, IL-6, IL-23, VEGF are under development. Recently, vaccination against IFN-alpha was reported as promising in systemic lupus erythematosus. Despite drawbacks that should be discussed, this novel strategy is promising in a post-biologics approach of chronic diseases, besides other strategies such as cellular therapies.

JS-4-2-2 | DNA vaccines for the treatment of allergy

S. Furukawa

Drug Discovery Research, Astellas Pharma Inc.

Peanut allergy can be a fatal food-related allergy with potential of life-threatening anaphylaxis induced by trace exposure. The estimated prevalence in the US for peanut allergy is reported as 1.3% overall, 1.4% in children, and 0.6% in adults[1]. There is no currently approved treatment for preventing peanut-induced allergic reactions in the event of accidental ingestion. Currently patients manage their condition by strict allergen avoidance and carrying epinephrine auto-injectors for use in case of accidental exposure. In the case of children, this vigilance must also be maintained by parents, schools, and other guardians.

In January 2015, Astellas and Immunomic Therapeutics entered into an agreement to grant Astellas the exclusive license for the Japan territory to develop and commercialize ASP4070, currently under investigation and designed to treat allergies induced by Japanese red cedar pollen. Thereafter, in October 2015, both companies entered into an exclusive worldwide license agreement to the LAMP-Vax products for the treatment or prevention of any and all human allergic diseases. ASP0892 is a new DNA vaccine to treat peanut allergy based on the investigational LAMP-Vax platform. A Phase I clinical trial of ASP0892 in the US is ongoing. The Phase II clinical trial of ASP4070 in Japan is also ongoing.

Today, I would like to introduce the mechanism of action of LAMP-Vax DNA vaccine technology, preclinical results, and the current status of clinical studies.

Reference: 1. J Allergy Clin Immunol. 2011 Mar;127(3):594-602.

LS-2-1 | Overview of lysosomal storage disorders (LSD): Recent advances of the treatment

Y. Eto[1,2]

[1]*Advanced Clinical Research Center, Institute of Neurological Diseases, Kanagawa, Japan;* [2]*Tokyo Jikei University School of Medicine, Tokyo, Japan*

LSD is one group of genetic disorders caused by a deficiency of lysosomal acid hydrolase and consists of more than 50 different disorders. LSDs are clinically characterized by CNS symptoms, hepatosplenomegaly, bone involvement and others in which their clinical symptoms depend on their nature of storage materials.

The treatment of LSD is most advanced disorders among various genetic diseases. These are enzyme replacement therapy (ERT), cell therapy such as hematopoetic stem cell therapy, chaperon therapy or substrate reduction therapy (SRT) and gene therapy. ERT is currently a golden standard therapy for LSD. In Japan eight different LSDs such as Gaucher disease, Fabry disease, MPS I, II, IV, and VI, Pompe disease and acid lipase deficiency are now under ERT. Now, these disorders are now treated more than 10 years by ERT and the data demonstrated that ERT prolonged their life span and also raised QOL in these patients. Another novel therapy are small molecules such as SRT and chaperon therapy. These treatments are oral administration, but some limitations are also present. To treat CNS symptoms by blood brain barrier penetrating enzymes is also promising therapy for LSD, since more than 80% of LSD involve the CNS. Various gene therapy technologies using AAV, lentivirus vectors and also editing gene therapy are now developing. And several genetic diseases are now succeeding; these are adrenoleukodytrophy (ALD), metachromatic Leukodystrophy and mucopolysaccharidosis type II. However, early treatment is essentially necessary. Therefore, newborn screening in these disorders now started in Pompe disease, Fabry disease and ALD. In this lecture, we present current advances these novel treatments in various LSD.

LS-2-2 | New drug development in rare diseases: evolution, challenges and paths forward

Y. Sato

R&D, JCR Pharmaceuticals, Japan

Although limited patient populations and complex pathophysiologies often render difficult the development of therapeutics for rare diseases, enzyme replacement therapy (ERT) for mucopolysaccharidosis(MPS), a significant component of Lysosomal storage disorders, has been an example where elucidation of underlying mechanisms of diseases has led to successful discovery of an effective treatment for the hitherto intractable congenital endocrinological disorders. However, Blood Brain Barrier (BBB), an intrinsic defence mechanism to protect the central nervous system (CNS) from large molecules, impedes the distribution of the administered enzymes into the brain, hence the CNS involvement in some MPS (neuropathic MPS) unaddressed by ERT, with resultant progressive cognitive decline, a devastating issue in clinical practice to date.

In order to deliver enzymes across BBB to overcome this therapeutic impasse, various efforts have been made, one of which is hereby introduced, i.e. fusion of deficient enzymes with anti-human transferrin receptor antibody (J-Brain Cargo; JCR Pharmaceuticals), with some promising clinical results in MPS-II (Hunter syndrome). This project represents interdisciplinary and international efforts encompassing basic research, translation and global clinical development for the neuropathic MPS sufferers around the globe.

An emerging trend in drug development across therapeutic areas is a more transversal R&D partnerships amongst, inter alia, pharmaceutical companies, academia and contract research organizations, since the cutting-edge knowledge and technologies, disease-specific expertise and operational excellence can no longer be covered by a single organization. In this regard, innovative research and development in rare disease area may be informative for other therapeutic areas to innovate the paths forward for R&D at large.

RS-4-1 | Macrophage and lymphocyte reprogramming in vitro for correction of an disturbed immune response in vivo

I. Malyshev; S. Lyamina; L. Kuznetsova; S. Kalish

Department, Moscow State University of Medicine and Dentistry named A.I. Evdokimov, Russia

Macrophages play a crucial role in the immunity. The proinflammatory M1 phenotype has bactericidal and antitumor properties, whereas the anti-inflammatory M2 phenotype has an antiparasitic properties, participates in tissue repair and angiogenesis. However it can promote tumor growth. When the microenvironment changes, macrophages can change their phenotype, i.e. reprogram themselves. We suggested and proved a hypothesis: there is the M3 switch phenotype, which in response to proinflammatory factors, as distinct from M1 and M2, induces the production of the anti-inflammatory cytokines and in response to antiinflammatory factors induces the production of the proinflammatory cytokines. We were able to form the M3 phenotype and use it to restore immunity disturbed by tumor. Many tumors produce anti-inflammatory cytokines, which reprogram antitumor M1 macrophages to protumor M2 macrophages. We showed that M3 macrophages, in contrast to M1, responded to protumor, anti-inflammatory cytokines by production of antitumor, proinflammatory cytokines and thus, preserved their antitumor properties. In vivo, the tumor disorders the antigen presentation and prevents formation of antigen-specific antitumor lymphocytes. We hypothesized that presentation of tumor antigens to lymphocytes by M3 macrophages in vitro, in absence of tumor cells, could result in an effective antitumor programing of the lymphocytes. M3 macrophages together with antigen-reprogramed lymphocytes resulted in complete inhibition of tumor growth both in vitro and in vivo. These data makes promising to develop a clinical biotechnology for eliminate the tumor by in vitro antitumor programing of the immune cells. We are confident that the M3 macrophages can help to restore the immune response disturbed in other pathologies, for example, in atherosclerosis or gout.

RS-4-2 | Biotherapy of gout inflammation: past and future

A. Pikhlak; V. Logachev; N. Mutyeva

FSBEI HE "A.I. Yevdokimov Moscow State University of Medicine and Dentistry" MOH Russia (MSUMD)

Gout is the disease with known etiopathogenesis. Clinical and laboratory manifestations of the disease allows to visually assessing the dynamics of the crystal-induced inflammatory process.

These features of the disease make possible to use it as a universal model (and in future potentially as a "gold standard") to study biotherapy aimed to suppressing the activity of pro-inflammatory interleukin 1β, which induce the differentiation of bone-resorbing osteoclasts from mononuclear precursors, and stimulating effects on osteoclasts, bone resorption and the destruction of articular cartilage through enhances the expression of extra-cellular matrix enzymes (collagenases and etc.).

Now Anakinra (IL-1Ra, recombinant protein, half-life—5 hours) and Canakinumab (Anti-IL-1β antibody, IgG1 mAb, half-life—26 days) are available to use in gout patients. In Russian Federation is ongoing Phase II study of RPH 104 for acute gout arthritis. RPH-104 is a heterodimeric fusion protein that binds with high affinity to IL-1β, also binds to IL-1Ra and IL-1α with lower affinity. Such investigations give opportunity to improve our view on the IL-1 role in general.

The new direction to relief the gout arthritis can be personalized medical biotechnology associated with the reprogramming of macrophages to create macrophages (M3) that produce anti-inflammatory

interleukins and thereby contribute to the resolution of inflammation. The proposed biotherapy may be effective for the treatment of crystal-induced inflammation in pseudogout and hydroxyapatite arthropathy, as well as atherosclerosis and diabetes mellitus.

RS-4-3 | Gout simulation in vivo and in vitro: the key points

S. Lyamina; S. Kalish; L. Kuznetsova; S. Mashina; I. Malyshev

Moscow State University of Medicine and Dentistry, Moscow, Russia

One of the key insights of gout formation is inflammatory reaction induced by the deposition of monosodium urate (MSU) crystals in the joints and soft tissues that can produce acute or chronic arthritis. Despite the fact that hyperuricemia is the main pathogenic defect in gout, many people with hyperuricemia do not develop gout or even form uric acid crystals. In this regard, it seems relevant to study the pathogenetic features of gout in order to identify the main steps and key points of influence to improve the outcome and disease prognosis in patients. Currently, a number of crystal-induced gout models have been proposed both in vivo and in vitro. One of the pivotal points in gout simulation is not only the direct injection of MSU-crystals into different anatomical structures; but reflection of a true diarthrodial joint microenvironment in which an acute gouty attack takes place. Concentration of urate and cation levels of microenvironment can vary and this can cause changes in crystallization degree, size or packing of the crystals. This can greatly influence crystal interaction with synovial cell lining and residential inflammatory cells, leading to an acute gouty flare. Gout inflammation greatly depends on several mechanisms, including coating of MSU crystals with proteins and clearance by differentiated macrophages, neutrophil apoptosis, clearance of apoptotic cells, inactivation of inflammatory mediators, and the release of anti-inflammatory mediators. Thus, generating in vivo and in vitro gout models should consider significant pathogenetic features that allow a more detailed study of the molecular and cellular mechanisms of gout pathogenesis.

JS-5 | Recent advances in psoriasis therapy

H. Mizutani

Mie University Graduate School of Medicine, Japan

Psoriasis is a chronic recurrent inflammatory skin disease that affects approximately 2% of the world population, but has a lower prevalence in Asian countries. There are several subtypes of psoriasis. Psoriasis vulgaris represents nearly 90% of all subtypes of psoriasis. Psoriasis vulgaris is diagnosed by the presence of characteristic skin manifestations with white scales, typical histopathological findings and the lack of disease specific laboratory markers. During the disease exacerbation, psoriasis is characterized by generalized pustular lesions and erythrodermic changes in association with systemic inflammatory response. Another serious complication of the psoriasis-associated systemic inflammatory response is seronegative polyarthritis: psoriatic arthritis (PsA), which occurs in 10%-30% of the patients at some point in the course of the disease. PsA involves joints of the fingers, extremities and spinal joints, and impairs the daily activities of the affected patients.

The pathogenesis of psoriasis has been the focus of many investigations for more than half a century, but it remains an unsolved mystery of dermatology in this 21st century.

In the last three decades, the involvement of a complex network of inflammatory cytokines has been reported in psoriasis. Over the last 10 years, the biologics for TNF-alpha, IL-12/23, IL-17 and IL-23 became available for daily clinical practice in Japan. The clinical efficacy of these therapeutic agents improved QOL of the patients, and may provide clues on the specific role of cytokines in the psoriasis cytokine network.

Here we present an overview on psoriasis, its current therapeutic options and future therapeutic perspectives.

JS-6 | Current anti-TNF therapy and the therapeutic potential of the IL-17A vaccine in ankylosing spondylitis

T. Tomita; H. Hayashi; J. Sun; H. Nakagami

Department of Orthopedic Biomaterial Science/Department of Health Development and Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Ankylosing spondylitis (AS) is a type of spondyloarthritis with unknown cause that affects young adults, with the age at onset ranging from the teens to the 30s, and causes chronic, progressive inflammation that primarily involves the axial skeleton, namely the spine and the sacroiliac joints. In its advanced stages, AS causes bony ankylosis and joint destruction not only in the spine but also in the appendicular skeleton, resulting in severe disability. The course of AS is progressive and involves pain and permanent dysfunction, which imposes significant physical, financial, and psychological burdens on family members as much as the patient. Anti-interleukin-17 (IL-17) therapies in addition to anti-tumor necrosis factor (TNF) therapies have been demonstrated to be effective, and are currently being tested AS in clinical trials. Therapeutic vaccines for diseases including Alzheimer's disease aimed primarily at inducing antibody production have been developed internationally in recent years, one of which is a therapeutic vaccine that we have developed with targeting IL-17A. The figure shows the basic design of the vaccine. This peptide vaccine incorporates a partial sequence of IL-17A as an antigen fused to a carrier protein such as keyhole-limpet hemocyanin, and is administered intradermally along with an adjuvant. Taking advantage of the fact that IL-17A is a self-protein, the vaccine is designed so that it induces humoral immune responses to produce anti-IL-17A antibodies without activating cellular immune responses. Multiple administration of this

vaccine was demonstrated to increase anti-IL-17A antibody titers in rats. Long-term, continuous therapy is required in spondyloarthritis, for which a long-term, stable IL-17A vaccine therapy is considered effective. The indication of the IL-17A vaccine is currently being tested using a rat model created by crossing a human HLA-B27-overexpressing rat and a β2 microglobulin-overexpressing rat to validate efficacy. This rat model displays arthritis and spondylitis, and the preliminary results demonstrate therapeutic effects in those rats to which the IL-17A vaccine is administered.

JS-7 | Optimal use of biologics in inflammatory bowel disease

M. Saruta

Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Jikei University School of Medicine, Japan

In Asian countries especially in Japan, the number of IBD patients is dramatically increasing. The number of UC and CD patients in Japan in 2014 was more than 180,000 and 40,000 respectively.

The characteristic feature of UC is classified in pancolitis type, left-sided colitis type, and proctitis type, and the characteristic feature of CD is also classified in small bowel type, colonic type, and ileocolonic type. At present both disease is incurable disease, therefore the treatment strategy is to achieve remission and maintain a complete remission.

The clinical stratification of UC is classified in mild (more than 60%), moderate (approximately 30%), and severe to fulminant (<5%). Therefore, it is very important to suppress mild to moderate active UC by medications such as mesalazine and corticosteroids at outpatient clinic. Medical management of UC refractory to corticosteroids is limited to IFX, ADA, GOL, tacrolimus, and cyclosporine. Recently, surgical treatment ratio for UC is decreasing dramatically because the efficacy ratio by anti-TNF-alfa antibody is extremely positive results. Anti-TNF antibody is also useful for corticosteroid refractory CD and can achieve complete clinical remission. Anti-TNF-alpha antibody seems to be a kind of miracle medicine because it works so quickly to achieve complete remission with mucosal healing. Accordingly, IBD patients with sustained remission can keep stable condition and can recover quality of life.

In this session, I will present how to evaluate, treat, and manage IBD such as UC and CD from the aspect of internal medicine, and also will show optimal use of biologics in IBD.

JS-8 | Potential immunotherpies for Parkinson's disease as a protein conformation disorder

N. Hattori

Department of Neurology, Juntendo University, Japan

The first known recognition of what we now call PD was by one of the greatest minds of all time, Leonardo da Vinci. Parkinson's disease (PD) is one of the most common movement disorders such as bradykinesia, tremor, and rigidity, while the main cellular pathological features include neuronal degeneration along with inclusions called Lewy bodies (LBs), and neuronal loss in the substantia nigra (SN). Although the exact mechanisms of PD remain to be elucidated, monogenic PD forms provide us a good hint to clarify the mechanisms of PD. Recently, it has been proposed that PD may be one of prion disorders. Therefore, we investigated the speed of a-syn transmission, which has not been a focus of previous a-syn transmission experiments, and whether a-syn pathologies spread in a neural circuit–dependent manner in the mouse brain. We injected a-syn preformed fibrils (PFFs), which are seeds for the propagation of a-syn deposits, either before or after callosotomy, to disconnect bilateral hemispheric connections. In mice that underwent callosotomy before the injection, the propagation of a-syn pathology to the contralateral hemisphere was clearly reduced. Thus, immunotherapies such as antibodies for a-syn may also be effective for this disease. Antibodies may have potential for clearance and blocking against a-syn. Even in neurodegenerative diseases, medical bio is considered to be the next generation treatment target.

ES-1 | The diagnosis and treatment of rheumatoid arthritis—a discussion on the clinical potential of a fully-human anti-IL-6R monoclonal antibody (sarilumab)

M. Kishimoto

Immuno-Rheumatology Center, St. Luke's International Hospital, Japan

We have seen significant advances in the treatment of rheumatoid arthritis (RA), for which accurate diagnosis is critical. This session begins with a discussion of key clinical findings to note in daily practice in the differential early diagnosis of RA.

In terms of therapy, the market for tumor necrosis factor (TNF) inhibitors, currently being chosen as first-line therapy for RA, is now saturated with five products. On the other hand, following the approval of a first product in the class of interleukin 6 (IL-6) inhibitors, a second product has been eagerly awaited. On November 22, 2017, sarilumab (trade name Kevzara, available as 150 mg and 200 mg prefilled syringes for subcutaneous injection), a fully-human anti-IL-6R monoclonal antibody (sarilumab), was added to Japan's NHI drug price list, and subsequently launched in February 2018 as the second IL-6 inhibitor. Approval in Japan lagged approximately one year behind overseas markets including Canada, the U.S., and Europe.

Sarilumab is similar to tocilizumab in that it binds to IL-6 receptors. IL-6 is involved in a range of physiological activities including inflammatory responses, induction of differentiation and growth of different types of cells, regulation of immune responses, and stimulation of platelet production, and has been strongly implicated in the pathogenesis of RA. Sarilumab inhibits the inflammatory activities of IL-6, thereby reducing joint inflammation and potentially improving the general symptoms of RA (including functional impairment resulting from joint deformity and destruction, fatigue, anemia, and osteoporosis, etc.). One feature of Kevzara is that it is offered in two approved doses: 200 mg and 150 mg. For the treatment of patients who have had an inadequate clinical response to one or more antirheumatic drugs, it is indicated to be administered at a dose of 200 mg once every two weeks as a subcutaneous injection, with possible reduction of the dose to 150 mg once every two weeks depending on the patient's condition.

The efficacy of sarilumab has been sufficiently demonstrated in clinical trials both in Japan and overseas, with clinical responses observed as early as two weeks after the first dose, as combination therapy in patients with RA who had an inadequate response to methotrexate (MTX) (the international multicenter MOBILITY Study and the Japanese KAKEHASI Study), as combination therapy in patients who had an inadequate response to TNF inhibitors (the international multicenter TARGET Study), and as monotherapy (the international multicenter MONARCH Study and the Japanese HARUKA Study). Reported adverse drug reactions include nasopharyngitis (13.2%), neutropenia (12.3%), injection site erythema (8.6%), and stomatitis (5.2%), and serious adverse drug reactions include infections, agranulocytosis, leukopenia, neutropenia, thrombocytopenia, intestinal perforation, shock, anaphylaxis, pneumonia interstitial, and hepatic function disorder. No new safety information has been reported that has not been previously reported with tocilizumab, which has the same mechanism of action as sarilumab, and there has been no evidence of an association between decreases in neutrophil counts and risk of infections. Sarilumab has also been shown to have low immunogenicity.

As with other biological therapies, Sarilumab is to be used with caution in patients with an active or suspected infection. In particular, patients with a prior episode of tuberculosis (patients with previously treated tuberculosis or with chest X-ray findings suggestive of latent tuberculosis) should be closely monitored, such as through periodic chest X-ray examinations for signs and symptoms of tuberculosis due to possible risk of reactivation.

LS-3 | Education program of rheumatology in Japan, EU & US and safety use of biologics in training hospital

M. Okada

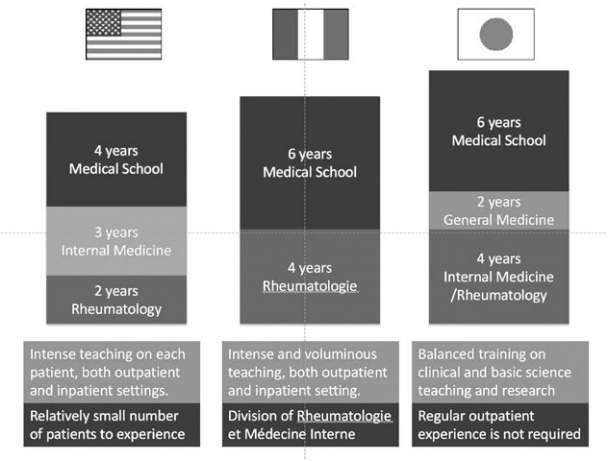
Immuno-Rheumatology Center, St. Luke's International University Hospital, Japan

Background: Systematic training of rheumatologists is imperative for the safe use of biologics. Biologics played roles in recent advancement of treatment of rheumatoid arthritis and other systemic autoimmune rheumatic diseases, however meticulous assessment of side effects are critical. Training program should include education, not only how to treat, but also how to monitor adverse events.

Materials and methods: Quality indicators including tuberculosis, hepatitis B virus and malignancy screening, immune function evaluation, periodical radiological surveillance are followed and feedback was given to improve systematic care.

Results: In general, quality indicators surveillance and feedback improved over the course of surveillance and serious complications were relatively low in comparison to previous reports. At the end of study, performance rate of tuberculosis and hepatitis B screening No tuberculosis, pneumocystis infection, reactivation of hepatitis B occurred.

Conclusions: Quality indicators are effective tool in education of rheumatology outpatient training.



GS-1-1 | Cybernic treatment using the cyborg-type robot Hybrid Assistive Limb enhanced functional regeneration in patients with rare incurable neuromuscular diseases (nanbyo)

T. Nakajima

Niigata National Hospital, National Hospital Organization, Department of Neurology and Rehabilitation Medicine, Japan

Prof. Sankai (Tsukuba Univ. & CYBERDYNE Inc.) and my clinical research team developed the cyborg-type Hybrid Assistive Limb (HAL) as a new treatment device for gait impairment, based on cybernics. Cybernics is an emerging field of assistive technology which aims to connect robots physically and electrically with humans. Cybernics was coined from cybernetics, mechatronics, and informatics by Prof. Sankai. We undertook a randomised clinical trial (NCY-3001) for gait treatment in patients with incurable neuromuscular diseases. The trial tested the efficacy and safety of cybernic treatment using HAL in severe and vulnerable “nanbyo” patients.

This cybernic treatment, which we provide, can enhance intention-based functional regeneration of the neural synaptic network and has the potential to be combined with drug, antisense-oligonucleotides, monoclonal antibody and stem cell therapies to achieve the maximum improvement effect. It has the potential to become a revolutionary combined therapy in the near future. Cybernic treatment also has the potential for the treatment of all voluntary movement disorders.

NCY-3001 trial for neuromuscular diseases has been completed. In Japan, HAL was approved as a new medical device in 2015 accordance to this data. Cybernic treatment using HAL began to be covered by Japanese health insurance in 2016. Subsequent clinical trials for other neurological disorders, including HTLV-1 associated myelopathy and hereditary spastic paraplegia (NCY-2001) and recovery phase of stroke (HIT-2016), are now being conducted. Multiple sclerosis and Parkinson's diseases are the next potential research candidates.

Cybernic treatment using HAL may become a new standard treatment for all neurological ambulation disorders. It is not an approach that is beyond therapy nor transhumanism.

GS-1-2 | Diagnostic functional statement of dental system

E. A. Solovykh

Prosthodontic department of Federal state autonomous educational institution of higher education I.M.Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation, Russia

Diagnostic of the functional statement of the dental system is one of the most difficult and discussable issue of the modern dentistry. This research was focused on the functional statement dental system as a postural sensor and its influence on the postural balance. Material and methods. 251 people 129 males and 122 females from 18 to 60 years ages were examined for postural balance, chewing muscles bioelectrical activity, autonomous nervous system activity. and electro cardiac activity. The functional state parameters for both the groups were analyzed by factor and cluster analysis. The results of the factor analysis allowed developing some theoretical aspects of the postural balance regulation. According to these results, new aspects of the genesis sub- and decompensation state in postural system were discovered. According to the results—dental system is one of the secondary sensor of the postural system which has 3%-2% Cumulative Eigenvalue from the whole postural system. The results of factor analysis revealed most informative parameters of stabilometry and their average values can be recommended for the clinical dentistry for diagnostics of dental systems' functional statement. According to the cluster analysis were obtained two groups of patients—first with compensated functional statement and second with sub-and decompensated functional statement. Finally, were created the computer system of diagnostics functional dental system that based on the analysis functional parameters dental and postural systems.

GS-1-3 | Innovations in measurement technologies in the field of rehabilitation medicine

M. Mukaino

Department of Rehabilitation Medicine I, School of Medicine, Fujita Health University, Japan

Recently, a number of reports have described innovative interventions, such as robotics and neuromodulation techniques, in the field of rehabilitation medicine, providing strong evidence for the efficacy of these interventions to improve motor function. A precise and objective means of evaluation of the results could elucidate these mechanisms in detail. If essential aspects of the clinical problem can be specified using precise measurements, a more targeted intervention to solve patients' problems should be possible. In this talk, the newly developed measurement technologies, including a system for activity monitoring using "smart" clothing and a clinician-friendly three-dimensional gait-analysis system, are introduced. The smart clothing system (the hitoe® system) is embedded with nanofiber technology to monitor the wearer's heart rate and estimate the patient's posture with accelerometer data. A study using the hitoe® system to monitor the activity of rehabilitation inpatients will be presented. The clinician-friendly three-dimensional gait-analysis system will also be introduced, including development of a simplified measurement system, preparation of various measures for safety, clinician-friendly ways of data presentation, and a data-analysis strategy combined with suggestions for intervention, which should facilitate the use of motion analysis in rehabilitation clinics. Further, the use of these measurement technologies to understand the mechanism of robotic rehabilitation will be discussed.

RS-5-1-1 | Clinical and epidemiological differences of chronic non-bacterial osteomyelitis in Russian federation

M. M. Kostik[1]; A. Y. Mushkin[2]; V. I. Zorin[2]; M. A. Makhova[1]; E. N. Suspitsin[1,3]; K. Okamoto[4]; H. Takayanagi[4]

[1]Saint-Petersburg State Pediatric Medical University, Saint-Petersburg, Russia; [2]Science research Institute of Phthisiopulmonology, Saint-Petersburg, Russian Federation; [3]N.N. Petrov Institute of Oncology, Saint-Petersburg, Russian Federation; [4]#Department of Immunology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, JAPAN

Background: Data about incidence and prevalence of chronic non-bacterial osteomyelitis (CNO) in Russia is scarce. The aim of our study was to evaluate clinical features and prevalence of CNO in Russia.

Materials and methods: The diagnosis of CNO was made with criteria, proposed by Jansson (2007, 2009), after the exclusion of other causes of bone disease. Our cohort consists of two main subtypes: (a) CNO, associated (n = 20) and not associated (n = 76) with rheumatic or immunopathological diseases. In the last group we identified the unique subgroup of patients with Dagestan origin (Fig. 1).

Results: this unique subset of patients, characterized by (a) early onset; (b) all children were initially diagnosed as having tuberculosis (TB) due to bone morphology findings (granulomatosus, e.g. tuberculosis-like inflammation), but had negative TB culture test; (c) initial treatment with combination of 3-4 anti-MBT drugs during 1-2 years was ineffective, patient continued to form new inflammatory bone foci; (d) patients had more severe clinical and radiological signs of disease, compare to others and (e) all patients have Dagestan origin and live in the Republic of Dagestan (area with high prevalence of consanguinity). Patients with Dagestan origin have earlier onset age, high foci number, high prevalence of symptomatic arthritis, femur and foot involvement.

Conclusion: We have found the unique regional subtype of CNO in Dagestan with at least 9 times higher prevalence, not detected in other parts of Russia. Further genetic investigations are intended.

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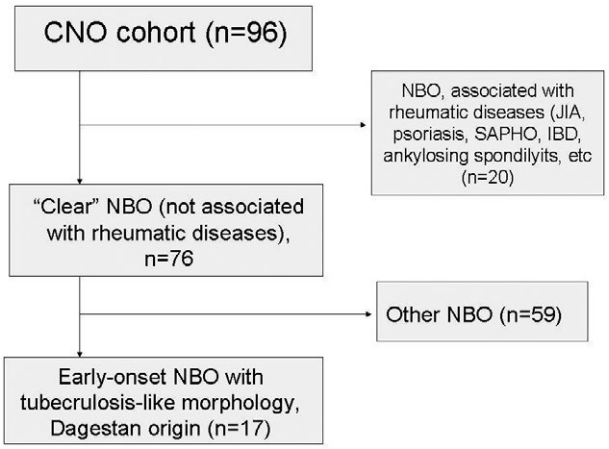

RS-5-1-2 | Surgical procedure in diagnosis and treatment of spinal form of non-bacterial osteomyelitis in children

A. Y. Mushkin[1]; A. S. Maletin[1]; M. M. Kostik[2]; O. L. Kopchak[3]; V. I. Zorin[1]

[1]Federal State Budget Institute "Science research Institute of Phthisiopulmonology", Saint-Petersburg, Russia; [2]Saint-Petersburg State Pediatric Medical University, Saint-Petersburg, Russia; [3]Kirov's regional children's hospital, Kirov, Russia

Introduction: The indications for surgery in pediatric patients with chronic non-bacterial osteomyelitis (NBO) are not clear especially in patients with affected vertebrae.

The aim: To establish the indications for diagnosis and treatment of spinal form of NBO (SpNBO).

Materials and methods: Thirty-two patients with vertebral lesion selected from more than 100 patients aged below 18 years with NBO established by complex of clinical, radiological and laboratory tests.

Results: Diagnosis: 30 of 32 spinal cases were associated with peripheral skeleton lesion. These patients underwent peripheral bone biopsy (closed transcutaneous or open) followed by morphology and bacteriological study. 2 patients underwent transpedicular vertebral body biopsy because of the isolated spinal affects.

Treatment: 7 of 32 patients underwent spinal reconstruction due to severe orthopedic complications: the back-pain exceed 6/10 degree by VAS despite complex chemotherapy incl. bisphosphonates. The surgery included reconstruction 360° in 4 cases due to severe spinal instability and kyphosis progression. 3 patients underwent anterior fusion only due to vertebral body lesion without kyphosis. 25/32 patient had no indications for spinal surgery.

Conclusions: The indication for spinal surgery in NBO include a diagnostic biopsy isolated SpNBO form and spinal reconstruction in cases with spinal instability, severe back-pain and kyphosis.

RS-5-2-1 | Protein allergy and metal allergy. The evolution of autoimmunity concept in immunology

M. Goloviznin

Moscow State University of Medicine and Dentistry (MSUMD), Russia

The first decade of XXI century was characterized by the change of the paradigm of immune defense, which was previously understood as the protection of genetic constancy of the organism. The evolutionary immunology has shown that the elements of retroviral genome incorporated into the mammalian immune system millions of years ago contributed to the formation of adaptive immunity. Thus, a textual understanding of the role of immunity as a protection against genetically foreign information contradicts the immune system evolution, in which the foreign (viral) genetic material actively participated. The discovery of the innate immunity mechanisms, especially PAMPs and DAMPs, allowed re-formulating the immune paradigm as protection from potentially hazardous biomolecules and living objects. However, the biological nature of the "hazard signal" remains disputable. The PAMPs as evolutionarily conservative structures are structurally very similar on both pathogens and saprophytes. Most likely, the "hazard signal" of PAMPs has dual nature 1. Structural foreignness and 2. Microorganism "dangerous behavior" such as quick multiplication etc. The dual nature of the PAMPs/DAMPs "hazard signal", allowed also giving an explanation of "metal allergy" mechanism. Currently, it is shown that the development of allergic reactions depends not only on antigen or hapten chemical structure, but also on the size and surface properties of biological particles formed by the allergens. Thus, the role of some metals in the pathogenesis of contact and systemic Allergy may be due to their high ability to bind proteins and form microparticles of different sizes, which are recognized by the innate immune system as "hazard signal".

RS-5-2-2 | Local and systemic mechanisms of hypersensitivity to alloys of dissimilar metals

U. Pikhlak[1]; N. Udagawa[2]; V. Logachev[1]; V. Parunov[1]; V. Terentiev[1]

[1]*Moscow State University of Medicine and Dentistry named after A.I. Evdokimov*
[2]*Matsumoto Dental University*

Most dental materials are intended for long term use and thus long time exposure may sensitize patients, resulting in allergy appearance. One of the main allergic reactions found in dentistry include contact allergy to metals resulting mostly in oral pigmentation, burning mouth syndrome (BMS) and lichenoid reactions. A numerous studies investigated the association between various oral health effects of fixed prosthodontic appliances and presented contradictory results. Allergic reactions to high noble and noble metal alloy and to base metal alloys may differ. However, the issue of allergen tolerance and incompatibility of alloys of dissimilar metals and their interactions between each other still remains open. This review summarizes the existing problems and challenges in the growing use of various metal alloys in medical practice. The report will present the possibility of using 2 methods: Laser Correlation Spectroscopy (LCS) and Inductively Coupled Plasma Mass Spectrometry (ICP-MS) in terms of 25 metals and metalloids, including toxic heavy metals in the assessment of oral cavity condition change during the prosthodontic or orthodontic treatment. Also the results of the in vivo pilot experiment held to evaluate the expression of pro-inflammatory cytokines (Il-1, Il-6) in rabbits having specially designed metal structures in the oral cavity with the sequential creation of conflicting pairs of dissimilar metal alloys will be presented.

RS-5-2-3 | Human mineral and trace element status: personalized and population-based approaches

A. R. Grabeklis

Peoples' Friendship University of Russia (RUDN University), Moscow, Russia

Introduction: Trace elements and minerals play a significant role in maintenance of a healthy state of an organism. Consequently, disturbances in trace element and mineral status may result in the development of pathologic states and diseases. The set of changes in trace element and mineral status forms a trace element portrait of persons, which can be estimated and used as an information basis for prevention and treatment of diseases either at individual or population level.

Aim: To compare peculiarities of personalized and population-based approaches to prevention and treatment of element-dependent diseases.

Results: Population-based investigations are mostly directed to prophylaxis and generally deal with relatively healthy persons. This determinates preferable use of hair analysis over use of liquid samples such as blood, urine etc. Also, as a rule, this approach involves investigations of environmental samples such as local food, water or soil to determine factors which can affect elemental status. Correction measures can include pharmaceutical, nutritional and agricultural strategies. On the contrary, individual investigations mostly deal with ill persons or persons in a pre-illness state. This makes highly usable blood, urine and other specific samples and makes preferable the use of pharmaceutical strategy for correction of elemental status. Only personalized approach allows treatment of complex diseases such as autism.

Conclusion: Population-based approach to monitoring human mineral and trace element status is effective in case of environmental impact of natural or anthropogenic origin and for determining of risk groups; while for treatment of persons within the risk groups and in case of multifactorial diseases a personalized approach is necessary.

GS-2-1 | Personalization of targeted treatment for rheumatoid arthritis

E. V. Zhilyaev[1,2]

[1]*European Medical Center, Russia;* [2]*Rheumatology Department of Russian Medical Academy of Continuing Professional Education, Russia*

Background: Currently, 9 targeted disease modifying anti-rheumatic drugs (tDMARD) for the treatment of rheumatoid arthritis (RA) are available in Russia. This diversity poses a difficult task for the doctor to choose a drug for each individual patient.

Aim of the study: To identify the possibilities of personalization of targeted therapy for RA.

Methods: Data were extracted from Moscow Unified Arthritis Registry (MUAR). Inclusion criteria of MUAR:

- diagnosis of RA, according to ACR (1987) or ACR/EULAR (2010) criteria;
- persons receiving tDMARD for RA;

For the search for predictors of tDMARDs general efficacy were included all treatment episodes in which there was at least 1 visit not earlier than 6 months since the start of the drug. Two-step search for predictors included:

- preliminary selection of factors significantly correlating with target variable;
- backward stepwise variable selection in multivariate model.

Results: At the moment of data extraction 829 RA patients were enrolled in the registry. Search for predictors of tDMARDs general efficacy included 625 treatment events of 579 patients. Independent predictors of achieved DAS28 were sex, $P < 0.001$; age, $P < 0.001$;

duration of treatment, $P < 0.001$; pain in the cervical spine during the course of disease, $P = 0.002$.

Independent predictors of DAS28 remission achieving were clinical stage, $P = 0.001$; erosive disease, $P = 0.019$; type (acute or gradual) disease start, $P = 0.009$; duration of observation in the register, $P < 0.001$.

Most important predictors of different response to tDMARD were:

- smoking (in smokers lowest activity was achieved with abatacept (ABA), tocilizumab (TOC) and and rituximab);
- type of RA start (in patients with acute start lowest activity was achieved with ABA, the highest—with TOC. In patients with graduate start—lowest activity was achieved with TOC).

Conclusion: There is a wide range of indicators that may predict the effectiveness of tDMARD in general and individual drugs in particular. The most promising direction seems to be the search for predictors of different response to treatment. Such predictors can be smoking and type of RA start.

GS-2-2 | Current situation of rheumatic disease treatment in Mongolia

D. Zulgerel; D. Tsolmon; Z. Devshil; D. Nandin-Erdene; B. Lkham-Erdene

Rheumatology Division of Internal Medicine, School of Medicine, MNUMS, Mongolia

Rheumatology in Mongolia's Internal Medicine has been developing quite late, but diagnosis and treatment of rheumatic diseases has been improving in recent years. Looking at the present disease structure of our country, non-communicable diseases are predominant, and our national program is working to prevent cardiovascular, cancer, stroke and traumatic injuries. In our country's health statistics, there was no record of musculoskeletal disease until 1998, but since then it has been increasingly growing every year. In the previous history, rheumatic diseases has been associated for many years in the cardiovascular diseases system, which slow down the independent development of Rheumatology. In traditional medical terms, every single disease of arthritis is called rheuma, it also creates misunderstanding and caused rheumatic diseases treatment confusion.

In recent years, rheumatology has been developed as independent branch in Internal medicine, rheumatologic textbooks have been published and Mongolian Rheumatology Association has been introduced RA and OA guidelines and conducted training which have resulted in the use of DMARDs in treatment and the quality of the patient's lives is improving. However the use Biologics is just at beginning stage. In the future, there is a need for collaboration with developed countries in research and practice to develop rheumatic sciences in Mongolia's Medical Science.

GS-2-3 | Features of joint syndrome and treatment specifics in the population of Tajikistan

S. M. Shukurova; Z. D. Hamroeva; F. U. Qurbonova

Therapy with Cardiorheumatology Course, Postgraduate Health Education Institute in the Republic of Tajikistan

The article presents situational (SWOT) analysis based on several large rheumatologic studies implemented in the Republic of Tajikistan for the last 5 years. The results were evaluated from data on:

screening among adult population of Tajikistan (n-10694) around four regions of the republic, dedicated to identify joint complaints with engagement of 1078 medical university students;

survey among physicians (n = 274) of various specialties (therapists, rheumatologists, tra u matologists, surgeons, neuropathologists, family medicine spec i alists) with the aim to discover usual prescriptions practice in tr e atment of patients with complaints to articular pathology in Tajikistan. The dynamics of changes in doctors therapeutic preferences (201 3 and 2015) was assessed with consideration of "The National Protocol for Management of Rheumatic Diseases" implementation;

prevalence and complications from usage of non-steroid anti-inflammatory drugs (NSAIDs) in patients with rheumatic diseases and several data on basic therapy of rheumatoid arthritis.

The results are presented comparing data from evidence-based medicine directed to identify the ways to optimal introduction of effective techniques into the day to day practices of doctors. The analysis of articular complains in Tajikistan estimated that arthralgia in the knee and/or hip joints was observed in 48.3% of cases among the urban and 61.5% in the rural population. Correlation of arthralgias and age was observed. 23.3% of city residents and 27.3% of rural population responded positively to the questionnaire about the presence of swelling of the joints. Sex and age characteristics presented that the majority of female patients were recognized in the general cohort of persons with joints complains, while for each individual nosology, sexual selectivity was identified. The structure of rheumatic diseases in people with previously treated arthritis has been established, among them, patients with osteoarthritis and rheumatoid arthritis predominate. The nature and location of joint syndrome had its own characteristics connected to the type of rheumatic disease, sex and age of patients.

Analysis of doctors survey showed that in real clinical practice the majority (97.8%) consider necessary to use non-steroid anti-inflammatory drugs for treatment of joint complains. It was revealed that doctors widely use diclofenac (64% in 2013 and 48.6% in 2015), ibuprofen (38.2% and 37.3%), nimesulide (33.7% and 36.2%), and indomethacin (14.6% and 18.9%). Less common were lornoxicam, meloxicam (15.7% in 2013 and 18.4% in 2015) and coxibs (14.6% and 8.6%). While structure-modifying medicines (basic medications) were prescribed only in 7.8% of cases in 2013, and in 2015 this figure increased to 50.3%. Results of the analysis of local (intra-articular)

therapy showed that in 31% of cases glucocorticoid agents (hydrocortisone 6%, kenalog 11%, betamethasone 14%) were used.

In conclusion it has been estimated that non selective NSAIDs were the drugs of choice for treatment of patients with articular pathology in Tajikistan, while selective NSAIDs are not often considered in regards to their less accessibility. Basic drugs (structure modifying) were used less often, even though there was some shift towards increasing after the introduction of National Protocols for the Treatment of Rheumatic Diseases usage of biological agents in treatment of inflammatory diseases is still on the lowest level. Low adherence to methotrexate prescription (duration and doses are extremely inadequate due to low awareness of doctors) were revealed. As for the basic drugs of the next generations (inhibition of TNF, etc.) situation is deplorable, as they are not even presented in the country because of high cost and difficulties with registration in the republic as pharmaceutical companies are not interested to present this medications to the country with low purchasing power of the population.

Key words: SWOT analysis of rheumatic diseases in Tajikistan, joint syndrome, NSAIDs, structure modifying treatment

GS-2-4 | Clinical features of SAPHO syndrome

Y. Ishihara

Clinical Reserch Center, Japan Medical Research Foundation, Japan

Introduction: The synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome was proposed by Chamot et al in 1987. It is a concept of collective disease which share common characteristic symptoms such as osteitis with/without dermatological manifestations, therefore diagnostic criteria for SAPHO syndrome has overlap with the other similar diseases such as spondyloarthritis (SpA) including psoriatic arthritis (PsA). Because of its mixed clinical features, pathogenesis and relevant treatment remains under discussion. Object of this study is to report the clinical features and our empirical treatment of SAPHO syndrome especially pustulotic arthorosteitis (PAO) which is representative disease of SAPHO syndrome.

Material and method: We collected patient's information from medical records retrospectively in 4 medical centers.

Results: 99 cases of SAPHO syndrome and 98 cases of PAO were analyzed. Average age at diagnosis was 50 years old for SAPHO syndrome and 56 years old for PAO. Ratio of male were 14% for SAPHO syndrome and 19% for PAO. Osteitis preceded in 34% of SAPHO syndrome and 7% of PAO. Dermatological manifestations preceded in 59% of SAPHO syndrome and 60% of PAO. Osteitis and dermatological manifestations occur simultaneously in 7% of SAPHO syndrome and 22% of PAO. CRP was raised in 47% of SAPHO syndrome and 30% of PAO. NSAIDs, glucocorticoid, bisphosphonates, salazosulfapyridine, iguratimod, MTX, biological drugs, and biotin were used randomly and were useful.

Conclusion: To diagnose SAPHO syndrome or PAO when it only has osteitis is challenging but important. DMARDS and biological drugs are useful for SAPHO syndrome.

GS-2-5 | New insights into the pathogenesis of systemic lupus erythematosus: finding novel players and therapeutic targets

N. Shen

Renji Hospital, Shanghai JiaoTong University School of Medicine, China

Genetic and epigenetic components play the critical roles on the development of SLE. Recently we have defined functional variant in NCF1, encoding the subunit of the phagocyte NADPH oxidase (NOX2), as the putative underlying causal variant that drives a strong SLE-associated signal detected by the Immunochip in the GTF2IRD1–GTF2I region at 7q11.23 with a complex genomic structure. We show that the p.Arg90His substitution, which can cause reduced reactive oxygen species (ROS) production, predisposes to SLE in multiple populations. Our findings highlight the pathogenic role of reduced NOX2-derived ROS levels in autoimmune diseases.

A hallmark of SLE is high titers of circulating autoantibodies. Recent study identified a novel $CD11c^+$ B cell subset in aged female mice that is critical for the development of autoimmunity. However, the role of $CD11c^+$ B cells in the development of lupus is still unknown. We explored the function and regulation of this novel B cell subset. The number of $CD11c^+$ B cell and titer of anti-chromatin IgG2a was significantly increased in induced SLE mice model (cGVHD). In vitro study demonstrated that $CD11c^+$ plasma cells produced large amounts of anti-chromatin IgG2a upon stimulation. In vivo depletion of $CD11c^+$ B cells significantly reduced anti-chromatin IgG and IgG2a production. Moreover, T-bet expression was remarkably increased in $CD11c^+$ B cells during cGVHD. Knockout T-bet in B cell alleviated the progression of cGVHD. Finally, the percentage of $T\text{-}bet^+$ $CD11c^+$ B cells were significantly elevated in lupus patients, which are positively correlated with anti-chromatin levels and nephritis. our data demonstrated that $T\text{-}bet^+$ $CD11c^+$ B cells are critical for the anti-chromatin autoantibody production, which might be explored as a therapeutic target for rectifying the abnormally produced anti-chromatin in SLE.

LS-4 | Clinical research of fibromyalgia in Japan

C. Usui

Juntendo University Faculty of Medicine, Japan

Fibromyalgia (FM) is characterized by widespread musculoskeletal chronic pain, fatigue, poor sleep, frequent psychological difficulties, and multiple tender points on physical examination. Although neither the etiology nor the pathogenesis of this condition is fully

understood, FM appears to be a disorder of the central nervous system. Thus, we discuss herewith, brain imaging studies of patients with FM. Our study revealed brain regions with significant hyperperfusion associated with the default mode network. On the other hand, we found an association between the metabolism in the thalamus, lentiform nucleus, and parahippocampal gyrus and prognosis in patients with early stage FM. I will show the results of fMRI study. Finally, I will also present new research system using Researchkit.

JS-9-1 | The working life of the elderly and a sustainable social security system

J. Kawasaki

House of Representatives, Japan

According to the Report of Vital Statistics compiled by the Ministry of Health, Labour and Welfare, figures in 2005 reflect a society in which approximately one million people were born and approximately one million passed away; however, in 2017 approximately 950,000 people were born and approximately 1.3 million passed away. The declining population will increase at an alarming rate as we progress into the future, and countermeasures against issues in relation to an aging population and low birthrate will become increasingly important.

In view of the foreseeable long-term decline of Japan's labor force, in order to remedy the situation, it is necessary to re-examine the working style of women, the elderly, and younger generation, in addition to the utilization of foreign workers. It is essential to secure a workforce by maintaining a proper balance in combining these four groups.

Regarding the elderly, public pension payments have been extended to the age of 65, and it has become mandatory for companies to facilitate secure employment by extending the age of retirement from 60 to 65. Further, a re-employment system has been established. We are already witnessing a trend where persons beyond the age of 65 and over the age of 70 desire to work as long as they are in good health. We are entering a future, an era where people will determine their own retirement age dictated by one's own health.

Underlying the working life of the elderly is a sustainable social security system. Self-medication to protect one's own health is not only vital for the elderly to maintain a healthy life, but also necessary in terms of the financial burden of the government. In terms of generic drugs, the aim is to substitute over 80% as early as possible by 2020, and with the cooperation of medical institutions, pharmacies, pharmaceutical companies, and other entities, the use of generic drugs is being actively promoted. Biopharmaceuticals are currently being used to treat various diseases including cancer and areas of rheumatoid arthritis. While they have proven to be highly effective, there is an increasing burden of medical expenses for patients, as well as increasing pressure on government funding for medical care. In addition, we have approached the time to effectively utilize biosimilars for biopharmaceuticals.

In order to maintain the health of elderly persons, I believe that it is necessary to retain a balance by reducing the burden of medical expenses through the utilization of generic and biosimilar drugs, while simultaneously developing advanced medicines.

JS-9-2 | Toward bringing innovation in drug discovery to the world

Y. Hatanaka[1,2]

[1]*Japan Pharmaceutical Manufacturers Association (JPMA), Japan;* [2]*Astellas Pharma Inc., Japan*

The Japan Pharmaceutical Manufacturers Association (JPMA) has 71 R&D-oriented member pharmaceutical companies (as of May 1, 2018), who contribute to improving global health and welfare and to economic growth through innovative drug discovery that addresses patient needs and clinical needs based on R&D employing advanced technologies.

The JPMA lays out future directions in the pharmaceutical industry with a vision to be achieved by 2025. Along the vision, we strive to ensure that the importance of innovation in drug discovery is recognized by a variety of stakeholders, and to seek understanding of the challenges we face and how to overcome. We pursue, in particular, more efficient drug discovery through improvement of R&D infrastructure and pharmaceutical regulatory reforms, and ensuring the long-term stability of the drug pricing system.

Healthcare expenditure is expected to increase as population ageing accelerates in many countries including Japan. To assure that people can continue to receive the full benefit of high-quality health services, we are required to make our social security system sustainable by sharing the burdens equally among the parties concerned and exercising wisdom in using limited resources effectively.

Leveraging IoT and AI in R&D with the industry, government, academia, and healthcare professionals working in collaboration will enable to balance the extension of healthy life expectancy and control of expenditure, and will lead to the achievement of Society 5.0. Moreover, expanding these efforts into overseas countries as a healthcare model will contribute to meeting the Sustainable Development Goals (SDGs) set by the United Nations.

Although the environment surrounding the pharmaceutical industry varies by country, we continue our efforts in world-class, innovative drug discovery to address the needs of patients.

AB-1 | Improvement of X-ray research in unspecialized conditions (wards)

O. M. Alekseeva

Department of Radiology of Moscow state university of medicine and dentistry named after A. I. Evdokimov, Russia

Introduction: X-ray is a common diagnostic procedure in a multidisciplinary hospitals. In the available scientific literature, there are some studies of the radiography in unspecialized conditions. However, there are few aggregate data of these studies to date.

Purpose: Analysis of the results of radiography in wards and resuscitation rooms, performed in multi-purpose hospitals, with the aim of forming requirements to the class of equipment for radiography in the conditions of the ward.

Materials and methods: The results of X-ray in wards and resuscitation rooms of 5 hospitals have been analyzed. The research has been subjected to 4,081 radiographic studies for the period from 2015 to 2016. Studies in the wards have been conducted on X-ray machines of different classes with the same physicotechnical conditions of the survey. Radiography in wards and intensive care rooms has been performed more often in one projection in a recumbent or semi-sitting condition.

Results: During the analysis it was determined that in unspecialized conditions 75.0% of the shots fell to chest organs, studies of the musculoskeletal system were revealed in 22.0% of cases and abdominal organs were observed in 3%. Pathological changes were not detected for 2,221 patients, which amounted to 54.4%. It was found that the most frequent disease of the chest were pneumonia of various genesis, complicated by the presence of hydrothorax.

Conclusions: Based on the analysis of X-ray researches, the indications for the studies were refined and supplemented, medical requirements for X-ray machines for shooting under these conditions were formulated.

AB-2 | Altered TNF-alpha receptors co-expression in rheumatoid arthritis is associated with disease severity

A. Alshevskaya[1,2]; J. Lopatnikova[1]; O. Chumasova[1]; N. Shkaruba[1]; A. Sizikov[1]; A. Karaulov[3]; S. Sennikov[1]

[1]*Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russia;* [2]*Biostatisticsand Clinical Trials Center, Novosibirsk, Russia;* [3]*Sechenov University, Moscow, Russian Federation*

The aim of the study was to examine the expression level of type 1 and 2 receptors to TNFα (TNFR1/TNFR2) on individual subpopulations of peripheral blood actively involved in immunopathological processes in RA.

Methods: The study included 51 RA patients with different disease activity at the age of 22-77 years. Co-expression and number of TNFR1/2 were calculated for monocytes, B-cells, T-cells, as well as among: cytotoxic T-cells, T-helpers, activated $CD8^+$ and $CD4^+$ cells, memory T-cells and naive T-cells, and T-regulatory cells by flow cytometry analysis (BD FacsVerse, USA).

Results: Co-expression of TNFRs was found to differ significantly among studied subsets (Fig. 1).

For all studied subsets, the proportion of cells expressing only TNFR1 is minimal. In addition, co-expression of type 1 and 2 receptors to TNF-alpha has a synergistic effect for almost all cell subsets. Those, the association between disease severity and activity indexes and parameters of TNF-alpha receptor expression on immunocompetent cell subsets were studied. Correlations of co-expression parameters were found with the level of C-reactive protein; the presence of systemic manifestations and radiologic stage of arthritis.

Conclusion: Changing in the ratio of cells with different variants of TNFR co-expression among populations actively involved in the pathological process is associated with disease severity. Identified indicators can be of diagnostic importance for assessing the severity of the inflammatory process in RA.

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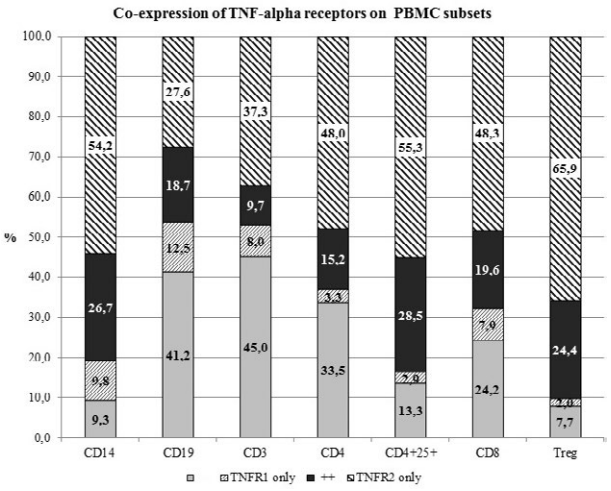


AB-3 | Danish stent is the modern way to endoscopic hemostasis in portal hypertension. Our clinical experience

A. A. Anisimov; A. V. Loginov

Kazan State Medical University, Russia

Goal: To analyze the innovative method of self-expanding nitinol stent use in the treatment program of acute variceal bleeding from the esophagus (AVB) due to portal hypertension (PH).

Methods: From 2013 to 2017 in Kazan clinical hospital № 7, we have treated 75 patients with AVB and patients with a high risk of AVB. The treatment program of 44 patients in the control group included Blakemore balloon tamponade. In 31 patients of the second study group, we used self-expanding nitinol Danish stents (DS) ("SX—Ella Danis").

Results: In the control group, we achieved the stable hemostasis in 33 (75.0%) patients, in 11 (25%) cases rebleeding began right after balloon removal. In the study group, 28 (90.3%) patients had stable hemostasis after DS use, only 3 (9.7%) rebleedings were observed. In control group complications appeared in 44 (100%) cases, in study group—in 8 (25.8%). The hospital mortality in the control group was in 25 (56.8%) cases. In the study group, we had 6 (19.4%) hospital deaths.

Conclusion: Innovative for Russia DS use is a progressive method to stable the hemostasis in patients with AVB due to PH. Moreover, the DS advantages over traditional Balloon tamponade also include low trauma effect (100%), good tolerance by the patient (93.5%); physiological saliva drainage (100%), constant fluid and food access (100%), the removal or displacement impossibility by the patient in a state of excitement. We assume DS should be used to stabilize the patient's condition and clarify the nature of the existing pathology.

AB-4 | Cardioprotective efficacy of N-terminal galanin fragments in ischaemia/reperfusion injury

G. Radik

Federal State Budgetary Institution "Scientific Medical Center of Cardiology" Ministry of Health of the Russian Federation, Russia

Purpose: The aim of this study was to evaluate ability of a modified galanin fragment (2-15) (WTLNSAGYLLGPβAH, G1) to limit acute myocardial infarction in rats in vivo. The natural galanin fragment (2-15) (WTLNSAGYLLGPHA, G2) and the complete rat galanin (1-29) (GWTLNSAGYLLGPHAIDNHRSFSDKHGLT, G3) were used as positive controls.

Objectives: (a) To evaluate the effect of peptides on hemodynamic variables: mean arterial pressure (MAP) and heart rate (HR). (b) To study the infarction limitation in myocardial ischaemia/reperfusion (I/R) injury, expressed as the percentage ratio of myocardial infarction to area at risk (MI/AAR). (c) To assess the activity of CK-MB and LDH in blood plasma at the end of experiment.

Results: The indicated doses of all peptides induced a decrease in MAP and HR within the first minutes after administration. By the end of reperfusion, these indices recovered to near baseline. The optimal doses of peptides G1, G2 and G3 (0.5 or 1.0 mg/kg) significantly reduced the percentage ratio of MI/AAR by an average of 40 ± 4%, 28 ± 3% and 41 ± 5% respectively, compared with the control. These effects were accompanied by a decrease in activity of CK-MB and LDH in blood plasma at the end of reperfusion compared with the control ($P < 0.01$).

Conclusion: The modified N-terminal fragment of galanin G1 mimics the cardioprotective effects of peptide G3 without affecting haemodynamic parameters. Its advantages over the natural peptide G3 are a simpler synthesis, high proteolytic resistance and better solubility. The results suggest that pharmacological ligands of GalR1-3 receptors may be a rational basis for the development of drugs for treatment of ischaemic heart disease.

AB-5 | Implementation of clinical decision support system for dosing in psychopharmacotherapy in patients with affective disorders based on the pharmacogenomic markers

M. S. Zastrozhin[1,2]; A. S. Sorokin[2]; E. A. Grishina[1]; E. A. Bryun[1,2]; D. A. Sychev[1]

[1]Russian Medical Academy of Continuous Professional Education of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; [2]Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare, Moscow, Russia

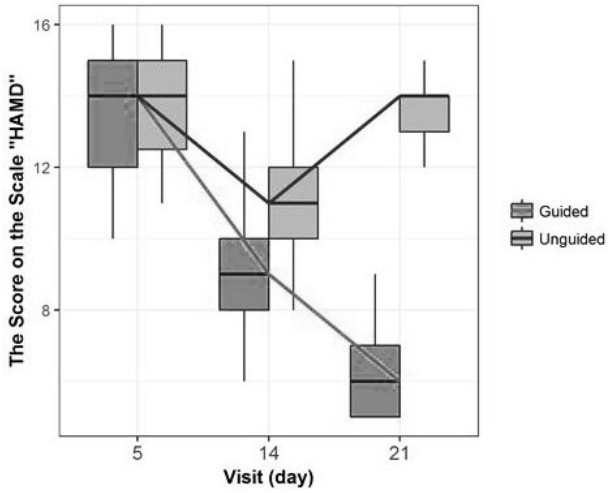
Background: Although pharmacogenetic tests provide the information on a genotype and the predicted phenotype, these tests themselves do not provide the interpretation of data for a physician. There are currently approximately two dozen pharmacogenomic clinical decision support systems (CDSS) used in psychiatry. Implementation of the clinical decision support systems capable of forming the recommendations on drug and dose selection according to the results of pharmacogenetic testing is an urgent task. Fulfillment of this task will allow increasing the efficacy of therapy and decreasing the risk of undesirable side effects.

Materials and methods: The study included 118 male patients (48 in the main group and 70 in the control group) with affective disorders and comorbid alcohol use disorder. To evaluate the efficacy and safety of therapy several international psychometric scales and rating scales to measure side effects were used. Genotyping was performed using real-time polymerase chain reaction with allele-specific hybridization. Pharmacogenetic test results were interpreted using free software PGX2 (www.pgx2.com).

Results: The total score on Hamilton Rating Scale by day 9 was 14.5 [14.0; 15.0] for the main group and 20.0 [18.0; 21.0] ($P < 0.001$) for the control group; by day 16 it was 14.0 [13.0; 15.0] for the main group and 14.0 [13.0; 14.0] ($P < 0.001$) for the control group (Figure 1).

Conclusion: Pharmacogenetic-guided personalization of the drug dose in patients with affective disorders and comorbid alcohol use disorder can reduce the risk of undesirable side effects and pharmacoresistance. It allows recommending the use of pharmacogenomic clinical decision support systems for optimizing drug dosage.

Figure 1. Dynamics of changes in Hamilton Rating Scale for Depression (HAM-D) scores across patients with different genotypes (data are presented as Me and IQR)



AB-6 | 3D-tumor spheroids in drug discovery

M. Kaviladze; V. Mironov

Sechenov Medical University, Russia

In these latter days special importance is played to in vitro models of preclinical drug testing based on cell cultures, including multicellular tumor spheroids (MTS) because of the tightening of requirements for animal experiments. The aim was to prove the advantage of the 3D model over the 2D model in order to further integrate the in vitro model of tumor spheroids into the design of anticancer drugs and to use primary tumor cells in drug screening studies for the implementation of personalized cancer treatment.

Methods : In this study, multicellular spheroids generated from a suspension of isolated cells of the immortalized human adenocarcinoma cell line MCF-7 were obtained in the serum. Microcapsules with MTS were incubated in 24-well plates with Methotrexate for 48 hours. The control group was presented by the monolayer MCF-7 culture (100,000 cells per well). Quantitative evaluation of the surviving cells was carried out with trypan blue dye in a Fuchs-Rosenthal counting chamber.

Results: The survival rate of viable cells in the control group was 2 times less than in MTS with a Methotrexate concentration of 100 nM. When Methotrexate concentration of 100 nM, the number of living cells was 65% and 88% for spheroids with size of 150 and 300 μm, respectively, while in the control group this value was only 35%.

Conclusion: Compared to monolayer cultures, cancer cells in 3D-spheroid cultures demonstrate greater resistance to cytotoxic drugs, with the cytotoxic effect of Methotrexate decreasing while MTS size increasing. In this regard, 3D-tumor models are a valuable “tool” for cancer research in the context of drug discovery.

AB-7 | Features of congenital malformations of parotid salivary gland in the etiology and pathogenesis of chronic parenchymal parotitis in childhood

A. Klinovskaya[1,2]

[1]*Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, department of pediatric maxillofacial surgery, Russia*

[2]*The dental pediatric surgery department of the Clinical Center of Maxillofacial and Plastic Surgery of Medical State University of Medicine and Dentistry named after A.I. Evdokimov, Russia*

Chronic inflammation of the parotid salivary gland (parotitis) occurs in clinics of pediatric surgery and CFH with a frequency of up to 92%-98% among all inflammatory diseases of the parotid salivary glands.

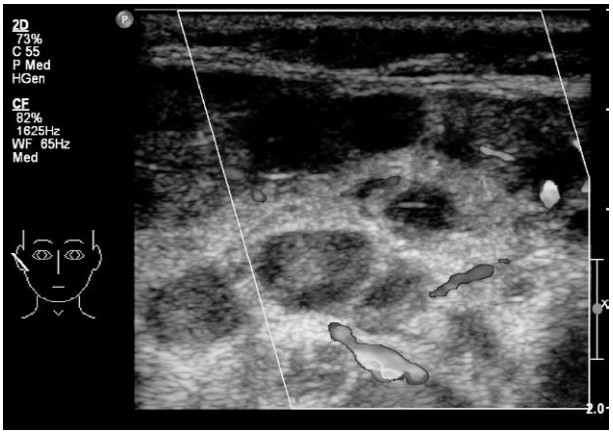
Objective: To study the congenital hereditary nature of chronic non-specific parenchymal parotitis in childhood.

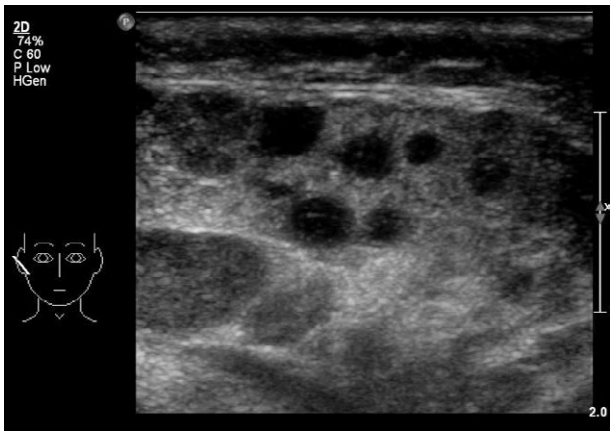
Objectives: (a) Analyze the main stages of diagnosis of CNPP; (b) Conduct an additional examination (ultrasound, contrast sialography) of parents of children with CNPP; (c) To examine relatives of 1 degree of kinship (parents) of probands (children with chronic mumps) -to conduct medical genetic counseling; (d) Standardize the method of diagnosis of children with CNPP; (e) Identify new prognostic risk factors, which characteristic of CNPP in childhood.

Materials and methods: During the period from 2015 to 2018 at the Department of Pediatric Maxillofacial Surgery on examination and treatment there were 111 patients (34 boys and 77 girls);between the ages of 6 months and 16 years.

After the medical-genetic counseling of 111 families, the following 3 types of inheritance of CNPP were identified. All patients and their parents underwent sonography.

Conclusions: Thus, after receiving and analyzing a large number of clinical, medical and genetic, echographic data in patients with CNPP and their family members, as well as control group data (healthy children and their parents), we first proved that chronic parenchymal parotitis—genetically determined and heterogeneous disease in etiology, clinical course and pathogenesis.





AB-8 | Fibrin clot growth and lysis modeling in hypertensive intracerebral hemorrhage: a pilot thrombodynamics assay study

I. Koltsov[1,2]; M. Martynov[1,2]; O. Brusov[1,2]; M. Faktor[1,2]

[1]*Pirogov Russian National Research Medical University, Moscow, Russia;* [2]*Department of Neurology, Neurosurgery and Medical Genetics of the Department of General Medicine, Russia*

Background: Non-traumatic intracerebral hemorrhage (ICH) is mainly caused by chronic hypertension. As hypertensive patients show abnormalities of blood coagulation [Catena et. al., 2000], they may play a significant role in ICH pathogenesis. The goal of this study was to evaluate the prognostic value of thrombodynamics assay in ICH patients.

Materials and methods: 19 consecutive patients with acute hypertensive ICH were included in the study. Patients with aneurysms, vascular malformations, blood coagulation disorders, and tumors were excluded. At admission, Glasgow Coma Scale score (GCS) and National Institutes of Health Stroke Scale score (NIHSS) were obtained, brain CT scan was performed, and thrombodynamics assay was carried out in coagulation and fibrinolysis modes using a T2 analyzer. 30-day survival was assessed using a telephone call. Thrombodynamics data were computed using Karmin software. Fibrinolysis potential (FP) was defined as the difference between areas under coagulation and fibrinolysis curves.

Results: A moderate statistically significant correlation between FP and NIHSS score at admission was found (r = 0.533, P = 0.019). Also, there was a negative statistically significant correlation between FP and GCS score at admission (r = −0.572, P = 0.011). FP was significantly different in survivors and in patients who died (49.2 ± 12.0 vs 65.0 ± 18.2 respectively, P = 0.035). In order to estimate the effect of FP on survival, a logistic regression was performed. After adjustment for sex, age, and systolic blood pressure, it was found that increased FP was associated with 30-day death (OR 1.136, 95% CI 1.012-1.275, P = 0.031).

Conclusion: FP is predictive of 30-day death in hypertensive ICH. The use of thrombodynamics may prove useful in the assessment of hyperfibrinolysis in ICH.

AB-9 | Results of treatment of patients in the remote period after revascularization of the brain

T. A. Kudryashova; A. A. Grin

Research Scientific Institute of Emergency named after N.V. Sklifosovskiy, Research Institute of Emergency, Russia

Purpose of research: To evaluate the results of treatment in patients in the long-term period after the imposition of extra-intracranial microanastomosis.

Tasks: (a) To evaluate the functioning of extra-intracranial microanastomosis using CT angiography. (b) To evaluate the linear and volumetric blood flow of extra-intracranial microanastomosis using ultrasound. (c) To evaluate the clinical picture of patients in remote period after the imposition of extra-intracranial microanastomosis Scales NIHSS, Rankin and Revermid. (d) To evaluate cerebral perfusion in the remote period after the imposition of extra-intracranial microanastomosis using ofect.

Results: In the Institute of JV to them.N. In. Sklifosovsky for 2013 and 2015. 129 patients with occlusion of the internal carotid artery were operated on. All patients underwent extra-intracranial microanastomosis between one of the branches of the superficial temporal artery and the cortical branch of MCA. According to our data, occlusion of the right ICA was observed in 58 patients, occlusion of the left ICA from 62 patients and occlusion of both ICA, in 9 patients. The majority of patients were enrolled in the planned order. The period of admission to the Department after the development of acute ischemic cerebral circulation disorders ranged from 1 day to 5 months. At admission, 48 patients had hemiparesis, speech disorders in 35 patients, hemiparesis and speech disorders in 18 patients, paresis of VII pair of PMH in 6 patients, without neurological deficit in 27 patients. All patients underwent additional examination. The clinical picture was assessed on scales of Riverbed, Rankin and NIHSS. ICA occlusion was confirmed by cerebral angiography, CT-AG or Mr-AG of the intracranial and brachiocephalic arteries. In preoperative preparation of patients underwent SPECT of the brain, examination by a neurologist, neuroophthalmology, radiography of chest organs, ECG, TCD, ultrasound, BCA, ECHO-KG. In all patients surgery was performed routinely. The average duration of surgery was 240 (140-420) minutes on average. Intraoperatively patients underwent TCD, the LDF and oximetry. In this case, LSCS for SMA averaged 15 (5-50) cm/s and according to flowmetry, the average volumetric blood flow for ICA was 90 (80-100) mL/min. In the postoperative period, there was no disturbance in the level of wakefulness. Postoperative control was performed using ultrasound, CT-AG, MP-AG and SPECT in the area of the anastomosis. In all observed cases, microanastomosis functioned and there was a positive trend according to ofect data. Postoperative complications were found in 5 patients. In 2 patients repeated of stroke in ischemic type in 1 patient—epiduralna hematoma in 1 patient, transient ischemic attack in 1 patient with pneumonia.

Results: Further analysis of observational data is required to fully assess the effectiveness of extra-intracranial microanastomosis. It

is planned to determine the functioning of extra-intracranial microanastomosis in the period of 1, 2 and 3 years after surgery. Using CT angiography, Doppler ultrasound, to assess the clinical picture of patients according to the scale NIHSS, Rankin and Rivermid, to assess brain perfusion using OFECT.

AB-10 | Efficacy and safety of BCD-020 as first-line biologic therapy in patients with active rheumatoid arthritis in clinical practice

D. Kusevich[1]; A. Avdeeva[2]; V. Rybakova[1]

[1]I.M. Sechenov First Moscow State Medical University (Sechenov University), Russia; [2]Nasonova State Institute of Rheumatology, Moscow, Russia

Objectives: To demonstrate clinical equivalence of clinical efficacy and safety a low-dose of BCD-020 as first-line biologic therapy in patients with active seropositive RA at previous RCT and in clinical practice.

Results: 20 patients with active seropositive RA for rheumatoid factors (90%) and/or anti-cyclic citrullinated peptide antibodies (100%), on a stable background regimen of methotrexate, were enrolled in the study. All patients received BCD-020 600 mg as an IV infusion on day 1 and day 15 as first-line biologic therapy. Patients basic characteristics were (median or %): age 61.5 years, 90% female, 4 years disease duration, 10 tender joints, 8 swollen joints, 14.4 mg/L CRP, 40 mm/h ESR. Median of basic RA activity for DAS28 (ESR) was 5.63: high 75% and moderate 25%. However DAS28-CRP values were consistently lower—the median was 3.28: high 25%, moderate 65% and low disease activity 10%. Disease activity by 24 weeks assessed by DAS28-CRP was 20% moderate, 20% low and 60% remission (DAS28-CRP < 2.5). Improvement in ACR20, ACR50, and ACR70 scores amounted to 75%, 45% and 15%, respectively. Treatment by BCD-020 resulted in rapid CD-19^{+} B-cell depletion by week 12, which was sustained for all follow-up period. No one of patient's experienced serious adverse events, at 15% indicated mild infusion reactions and no one level IgG decreased down 6 d/l.

Conclusions: The BCD-020 demonstrated similar efficacy, safety in real clinical practice to previous RCT. Further clinical values evaluation of cell's and tissue biomarkers and instrumental signs of inflammation is planned to improve the control of RA activity and efficacy of anti-B-cells therapy.

AB-11 | Computer planning and intraoperative control with using of computer navigation system in orthognatic surgery

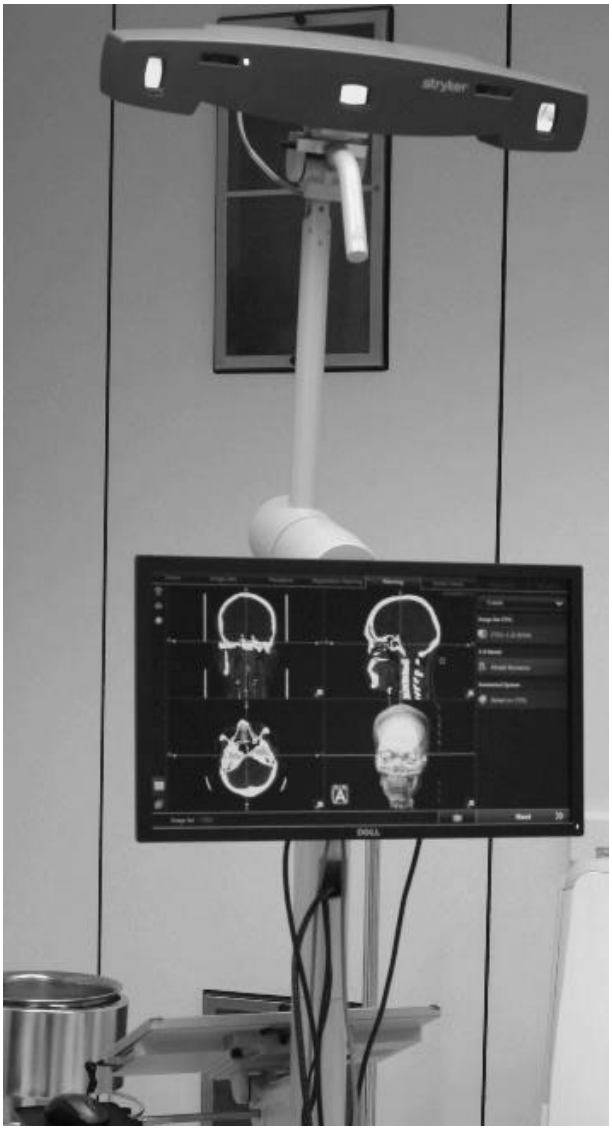
P. Mitroshenkov

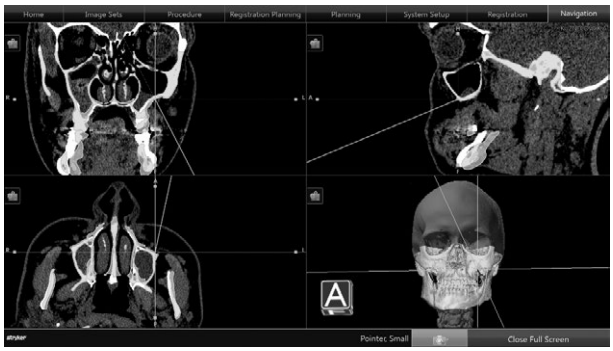
Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, department of maxillofacial and plastic surgery, Russia

Nowadays, the complex treatment of skeletal forms of malocclusions is an actual problem in maxillofacial surgery. The result of surgical treatment is defined by the restoring of aesthetic facial proportions. In the modern orthognatic surgery methods of intraoperative control with using of computer navigation are applied for minimization of subjective evaluation of osteotomized bone fragments positioning.

The aim of this study was to create an algorithm of preoperative planning and intraoperative control with using of navigation systems.

During this study, we have operated 25 patients with different congenital asymmetric deformations of facial skeleton. Preoperative





virtual simulation and intraoperative control were performed with using of Blender 2.79 software and optical navigation systems «BrainLab 18070 Kick», «CranialMap CMF Version 2.0» (Stryker) (Fig. 1). The intraoperative control of osteotomized bone fragments positioning was carried out by superimposing of reference points on the virtual model with points in the surgical wound (Fig. 2).

The analysis of preoperative virtual planning and postoperative CT-scans of patient's facial skeleton showed, that the application of intraoperative control with using of computer navigation has significantly improved the predictability of complex treatment results. The superimposing of postoperative 3D skull model with virtual model has revealed the discrepancy of linear measures (0.2 mm). This discrepancy was clinically acceptable.

The clinical and radiological analysis of surgical treatment of 25 patients has shown that:

- The intraoperative navigation control allows to increase the accuracy of osteotomized bone fragments positioning significantly.
- An optical instrument-based navigation systems allow to perform an intraoperative control no only reference points, but also the position of a working part of surgical equipment.

AB-12 | Orthopantomography as a screening tool for asymptomatic carotid disease

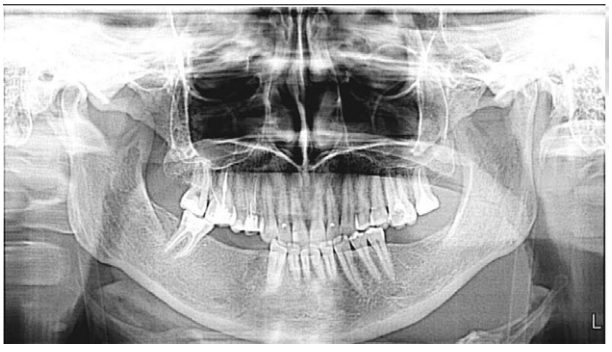
M. S. Starodubtseva; D. A. Lezhnev; I. D. Stulin

Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, department of radiology, Russia

Purpose and objectives: To evaluate the properties of carotid arteries calcifications (CAC) detection as a sign of asymptomatic carotid disease by orthopantomography (OPTG).

Results: Results of radiological examination of 1,291 patients in the age between 55 and 59 years old were analyzed by skilled radiologist. CAC were identified at OPTG in 12.6% (163 patients). Among them 115 (70.55%) were women and only 49 (29.45%)—men. The level of CAC wasn't detected in 53 cases (32.5%), in 1 (0.61%) case the level of CAC was at the body of C1 vertebra, in 2 (1.22%)—intervertebral cartilage between C1 and C2, in 1 (0.61%)—the body of C2, in 4 (2.48%)—intervertebral cartilage between C2 and C3, in 15 (9.2%)—the body of C3, in 38 (23.3%)—intervertebral cartilage between C3 and C4, in 39 (23.9%)—the body of C4, in 8 (4.96%)—intervertebral cartilage between C4 and C5 and in 2 (1.22%)—the body of C5. Certain predominance of unilateral lesions (145 cases—88.95%) was detected and among them left-sided changes were more prevalent (59.31%) than right-sided (40.69%). CAC mostly were single, crumbly, homogeneous and their size was less than 0.5 cm.

Conclusion: CAC could be detected by OPTG most likely as single, crumbly, homogeneous shadow at the level of C3, C3-C4 and C4 vertebrae. It has to become a promising screening trend which will help to reduce the risk of the atherosclerotic cerebrovascular complications of asymptomatic carotid disease.



AUTHOR INDEX