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Materials on successful workshop accomplishment including guidelines

Deliverable D5.1

VirA project No. 952376

Importance of differential diagnostic in rheumatic diseases

Project funded by the European Union		
Dissemination Level		
PU	Public	X
PP	Restricted to other program participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

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An international workshop “Importance of differential diagnostic in rheumatic and other autoimmune diseases” was organised by Rīga Stradiņš University under the EU-H2020 project VirA, in cooperation with partners from Germany and Israel. It was held online, in the Zoom meeting platform from the 29th till the 30th of September 2021.

The topics discussed covered a wide range of questions, from the actuality of autoimmunity in general and immune profiling in inflammatory, autoimmunity and infectious diseases till immune mediated ataxias, myalgic encephalomyelitis/chronic fatigue syndrome and multiple sclerosis in conjunction with Covid-19.

The workshop was introduced by Liene Ņikitina-Zaķe, Director of the Research Department of Rīga Stradiņš University, Latvia and Modra Murovska, Assoc. Professor, Project Coordinator from Institute of Microbiology and Virology, Latvia. Presentations were provided by qualified world and European specialists in the field of autoimmune diseases, including Prof. Yehuda Shoenfeld and Prof. Howard Amital from Tel Aviv Sheba Medical Center in Israel, Prof. Marion Schneider and Christian Scheiber from Ulm University in Germany, as well as MD, PhD Anda Kadiša, MD Mihails Tarasovs, MD, PhD Aleksejs Derovs, MD, PhD Ilze Konrāde and other professionals from Latvia.

Summary of the main ideas introduced in the workshop - Day 1

1) WHY AUTOIMMUNITY? by Yehuda Shoenfeld.

A wide range of topics were discussed in this presentation including the role of the HLA gene polymorphism in the development of autoimmune diseases. Author also presented and analysed the potential interaction between breast implant and autoimmunity, showing a potential association between HLA and silicone implants that serve as adjuvants for the hyperstimulation of the immune system. He also shared possible treatments of autoimmune

dysautonomia regarding silicone implants including active immunization, plasmapheresis, elimination of the cause (explanting the silicone, avoiding adjuvant) and passive transfer.

2) DIFFERENCES BETWEEN INFLAMMATORY AND NON-INFLAMMATORY ARTHRITIS by Anda Kadiša.

In this presentation the non-inflammatory arthritis was opposed to the inflammatory arthritis. As to the degenerative arthritis group, causes, symptoms and diagnostics of osteoarthritis, Charcot neuroarthropathy and ochronosis were introduced. In the inflammatory arthritis group, on the contrary, rheumatoid arthritis, systemic lupus erythematosus, seronegative spondyloarthropathies, ankylosing spondylitis, Reiter's syndrome, gout and pseudogout were reviewed and their typical characteristics were explained.

3) COVID-19 AS AN AUTOIMMUNE VIRUS by Yehuda Shoenfeld.

The author showed the genetic predictors of severe Covid-19, explained how the level of expression of angiotensin-converting enzyme (ACE) 2 in different tissues affect the organ damage. The pathogenesis of the cytokine storm, macrophage activation syndrome and sepsis in Covid-19 was explained. Moreover, the author gave an insight into the hyperferritinemic syndrome and the role of iron depletion therapy, as well as the interaction of Covid-19 and immune thrombocytopenic purpura, Guillain-Barre syndrome and Kawasaki disease. Actuality regarding vitamin D supplementation was emphasized and evidence of anosmia showed, explaining that it is a specific symptom that should be considered in evaluating isolation, testing and treating Covid-19. At the end of the presentation the mechanism of vaccines was explained and symptoms of post-covid-19 syndrome introduced.

4) CLINICAL EXPERIENCE ON OSTEOARTHRITIS AND CASE REPORT by Mihails Tarasovs.

Firstly, pathogenesis of osteoarthritis was explained and phenotypes introduced. Author showed that anxiety and depression adversely impact the quality of life of patients with osteoarthritis. Secondly, a clinical case was introduced, where a patient with calcium pyrophosphate dihydrate crystal deposition disease was presented.

5) AUTOIMMUNITY IN GASTROENTEROLOGY – WHAT IS HIDDEN? by Aleksejs Derovs.

The author gave an insight in the pathogenesis of pernicious anemia and its association with other autoimmune diseases, as well as explained the immune response mechanism in celiac disease, emphasized the growing incidence of inflammatory bowel diseases and explained which genetic predisposition is clinically meaningful in both Crohn's disease and ulcerative colitis. Possible triggers, pathogenesis, diagnostics and associated autoimmune diseases of autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis were also discussed. In the development of some of the above-mentioned pathologies the author also pointed out the role of the microbiome.

6) CLINICAL CASE REPORT - AUTOIMMUNITY IN GASTROENTEROLOGY by Zane Straume.

In this presentation a detailed case report was introduced, in which a patient with ulcerative colitis was examined. The conclusions the author emphasized were that it is important to appropriately investigate the patient and take a detailed medical history and that treatment

escalation should be monitored and administered gradually. Apart from that, the author also drew attention to the importance of a collaboration between a doctor and a patient and involvement of a multidisciplinary team that should be dealing with such complex medical scenarios.

7) **THYROID AUTOIMMUNITY: EXPLORING THE ROLE OF TH17-ASSOCIATED CYTOKINES AND PATHOMORPHOLOGICAL MECHANISMS INVOLVED IN THE PATHOGENESIS OF HASHIMOTO'S THYROIDITIS AND GRAVES' DISEASE** by Tatjana Zaķe.

Firstly, the pathogenesis of autoimmune thyroid diseases and genetic susceptibility was explained, secondly, the author talked about the mechanism and molecular mimicry behind infections and autoimmune thyroid diseases. Moreover, an association between Covid-19 and autoimmune thyroid diseases was shown. The predisposing factors to an autoimmune thyroid disease were identified, above which the author mentioned excessive iodine intake, infections, selenium deficiency and genetic predisposition. Although the author concludes that there are no differences in the levels of Th17-associated cytokines among patients with autoimmune thyroid diseases, the level of expression of Il-17 in the thyrocytes was found to be higher in patients with Grave's disease and Hashimoto thyroiditis.

8) **THE ROLE OF SELENIUM IN THYROID AUTOIMMUNITY** by Ieva Kalere.

By this presentation the author pointed out the growing prevalence of benign thyroid diseases with low selenium status in accordance to the potential danger recommending it as a supplement. One mechanism how the effects of selenium supplementation might be regulated is via the repletion of antioxidant or immune – modulating selenoproteins. These selenium supplements might as well be useful in Grave's disease to reduce the ocular involvement, but more research is needed to confirm it.

9) **UPDATE IN ENDOCRINE AUTOIMMUNITY** by Ilze Konrāde.

The speaker gave an insight into the etiology and risk factors of thyroid autoimmunity, the importance of iodine regarding the synthesis of thyroid hormones and their role during pregnancy and neuronal development. Interestingly, there has also been found a correlation between the iodization programs and autoimmune thyroid diseases. Apart from that, the presentation also covered the actual topic regarding the development of thyroid diseases in relation to Covid-19.

Summary of the main ideas introduced in the workshop (Day 2)

1) **AUTOIMMUNITY – FROM DIAGNOSIS TO TREATMENT** by Howard Amital.

Rheumatoid factor, citrullinated peptide, antinuclear antibodies, their titers, specificity and level in terms of a disease were analyzed. The author also compared different autoantibody pattern and changes in systemic lupus erythematosus and finished his presentation, showing an association between breast implants and autoimmunity, including the imbalance of G-protein-coupled receptor antibodies.

2) **ALGORITHM BY IMMUNE PROFILING AND BIOMARKERS TO IDENTIFY INFLAMMATORY, AUTOIMMUNE AND INFECTIOUS DISEASES** by Marion Schneider.

The author presented and introduced the algorithm how to distinguish such an ambiguous diagnosis as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and post-Covid-19 ME/CFS, showing three main metabolic phenotypes of this disease, it's metabolic effects and the role of epigenetic DNA modifications. The presenter shared her experience regarding specific blood tests that are useful to

recognize the above-mentioned patient groups, concluding that duration of the disease correlates with the biomarker panel.

3) CHARACTERIZATION OF EXTRACELLULAR VESICLES FROM INFLAMMATORY MACROPHAGES STIMULATED BY EXOGENOUS ATP AS A DANGER SIGNAL by Christian Scheiber.

The main conclusions of this presentation were that cultured macrophages react to ATP with extracellular vesicle (EV) release and/or cell death by forming pores and the EV that are released are composed of different size subpopulations. The author also updated the listeners with the fact that microRNA-packed AV could mimic an inflammatory state and that mixed response types have been identified due to various diagnostic patterns.

4) MS DISEASE MODIFYING THERAPIES AND COVID-19 (DISEASE OUTCOMES, VACCINATION) by Sandra Svilpe.

During this discussion the author tried to reply to 2 main questions regarding the disease modifying therapies (DMT) used to treat multiple sclerosis (MS), namely, whether the risk of infection with Covid-19 increased in neurologic patients and whether there is an increased or even decreased risk of a severe disease course in this patient group. A summary of the use of various DMTs, as well as recommendations in conjunction with the Covid-19 vaccination was given.

5) CHRONIC INFECTIONS AND LYME CONTRIBUTING TO AUTOIMMUNE DISEASES by Kunal Garg.

The author's research presented focused on three main patient groups: ME/CFS, fibromyalgia (FBM) and Alzheimer's disease (AD) and their autoantibody profiles. Moreover, the topic regarding Epstein-Barr Virus (EBV), Borrelia infection and the research plan used was reviewed. The author also mentioned the interaction between the EV derived from EBV and their ability to suppress dendritic cells in patients with gastric carcinoma and inhibit polarization of Th-17 cells in MS patients. To conclude with, the role of EBV and Borrelia infection in ME/CFS, FBM and AD was considered as not yet fully understood, EBV associated EVs was considered a possible trigger for the production of autoantibodies, as well as the use of deep immune profiling and machine learning were identified as possible diagnostic tools regarding autoimmune diseases.

6) SERUM NEUROFILAMENTS IN MULTIPLE SCLEROSIS by Daina Pastare.

The author presented a cross-sectional study held in Riga East University hospital, Latvia, in which 102 serum samples of MS patients and healthy controls were collected and the level of sNfL concentration measured. After giving the information regarding the research process, the conclusions of this paper were introduced, namely, that the serum level of NfL increased with age in all population groups but was higher for MS patients with severe functional disability and that higher serum level of NfL showed neurodegeneration with disease progression.

7) ATOPIC DERMATITIS - CURRENT ISSUES, PATHOGENETIC MECHANISMS AND EMERGING THERAPEUTIC PERSPECTIVES by Elga Sidhoma.

This presentation was focused on the latest information regarding the etiology, pathogenesis, immunological role of atopic dermatitis, as well as detailed analysis of the current literature regarding the above-mentioned disease. The author also gave an insight into the recommendations of the treatment methods, including the basic therapy, drugs that are used in case of a transient, recurrent and persistent eczema.

8) EARLY SKIN MALIGNANCIES AND THEIR TREATMENT OPTIONS WITH TOPICAL IMMUNOMODULATING AGENTS by Alise Balcere.

The author began the presentation with an insight into the interaction between the immune system and the development of melanoma and non-melanoma skin cancers, showing that immunosuppressed individuals have a higher prevalence of squamous cell carcinoma (SCC), as well as that SCC use to develop in the places of ulcers. The presenter also identified the risk factors for malignant transformations, including the age and ulcer duration. In the end the listeners were introduced to a research, in which long-term outcomes of imiquimod-treated lentigo maligna were analyzed.

9) IMMUNE- MEDIATED ATAXIAS by Ramona Valante.

This presentation shared an experience of a patient diagnosed with primary autoimmune cerebellar ataxia and the pathway which led doctors in Pauls Stradiņš Clinical University Hospital, Riga, Latvia to this rare diagnosis. The author also presented the latest information regarding the diagnostic methods of immune-mediated ataxias, as well as principles of treatment.

10) MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME by Santa Rasa-Dzelzkalēja.

The researcher provided an insight into a study with an aim to determine the involvement of human herpes virus-6 (HHV-6), human herpes virus-7 (HHV-7) and parvovirus B-19 (B19V) in etiopathogenesis of ME/CFS. Following a description of the study design some conclusions were made, more precisely, that markers of HHV-6, HHV-7 and B19V could be used as biomarkers in diagnosing ME/CFS, that persistent HHV-6, HHV-7, B19V coinfection in an active phase might influence evaluation of pro- and anti-inflammatory cytokines and that a higher load of HHV-6 and HHV-7 in patients with a more severe disease course advocate on the involvement of these viral infections in ME/CFS development.

11) TICK - BORNE ENCEPHALITIS AND AUTOIMMUNE OUTCOME – CLINICAL DATA OF LATVIA AND CASE REPORT by Ilja Drjagunovs, Angelika Krūmiņa,

As part of this presentation a case study of an 84 years old female diagnosed with tick-borne encephalitis virus induced anti-NMDAR encephalitis with profound cognitive and consciousness impairment was presented. Further on a theory-based explanation on the etiology, pathogenesis, immune system involvement, as well as the best treatment options available was given.

Participant evaluation of the workshop

1. What is your overall assessment of the event? (1 = insufficient - 5 = excellent)

[More Details](#)

[Insights](#)

23

Responses

4.57

Average Number

5. Knowledge and information gained from participation at this event.
-Met your expectations?

[More Details](#)

[Insights](#)

Yes	20
No	0
Somehow	3



6. Knowledge and information gained from participation at this event.
-Will be useful/applicable in my work?

[More Details](#)

[Insights](#)

Definitely	7
Mostly	11
Somehow	5
Not at all	0



7. Please comment on the organization of the event (from 1 = insufficient to 5= excellent)

[More Details](#)

[Insights](#)

23

Responses

4.39

Average Number

Conclusions

This meeting proves that highly valued and experienced professionals in their fields can interact with colleagues who are new to the field and enrich one another. The topics discussed were vary varied and provided the actual information regarding autoimmune diseases in neurology, rheumatology, gastroenterology, endocrinology and other fields of medicine.

Overall workshop was intended to raise the professional knowledge, as well as interest in autoimmune diseases in general and we are honoured that the aim was accomplished, which is proved by above-inserted info graphs showing that most of the participants met their expectations, as well as will be able to use the gained knowledge in their practical work.

Agenda of the workshop.

Workshop leader, Prof Angelika Krūmiņa

September 29, 2021	
10.00 - 10.15	<p>OPENING AND INTRODUCTION OF VirA PROJECT</p> <p>Liene Nīkitina-Zaķe, Director of Research Department, RSU, Latvia Modra Murovska, Assoc. Professor, Project Coordinator, Institute of Microbiology and Virology, RSU, Latvia</p>
10.15 – 10.50	<p>WHY AUTOIMMUNITY?</p> <p>Yehuda Shoenfeld, Professor, Tel -Aviv University, President of Ariel University, Israel</p>
10.50 – 11.35	<p>DIFFERENCES BETWEEN INFLAMMATORY AND NON-INFLAMMATORY ARTHRITIS</p> <p>Anda Kadiša, MD, PhD, Lead Researcher, Institute of Microbiology and Virology, RSU, Latvia</p>
11.35 – 12.10	<p>COVID-19 AS AN AUTOIMMUNE VIRUS</p> <p>Yehuda Shoenfeld, Professor, Tel -Aviv University, President of Ariel University, Israel</p>
<i>12.10 – 12.30</i>	<i>Break</i>
12.30 – 13.00	<p>CLINICAL EXPERIENCE ON OSTEOARTHRITIS AND CASE REPORT</p> <p>Mihails Tarasovs, MD, PhD student, Department of Internal Diseases, RSU, Latvia</p>
<i>13.00 - 14.00</i>	<i>Break</i>
14.00 – 14.45	<p>AUTOIMMUNITY IN GASTROENTEROLOGY – WHAT IS HIDDEN?</p> <p>Aleksejs Derovs, MD, PhD, Assoc. Professor, Department of Internal Diseases, RSU, Latvia</p>
14.45 - 15.15	<p>CLINICAL CASE REPORT - AUTOIMMUNITY IN GASTROENTEROLOGY</p> <p>Zane Straume, MD, PhD student, Department of Internal Diseases, RSU, Latvia</p>
<i>15.15 - 15.30</i>	<i>Break</i>
15.30 - 15.55	<p>THYROID AUTOIMMUNITY: EXPLORING THE ROLE OF TH17-ASSOCIATED CYTOKINES AND PATHOMORPHOLOGICAL MECHANISMS INVOLVED IN THE PATHOGENESIS OF HASHIMOTO'S THYROIDITIS AND GRAVES' DISEASE</p> <p>Tatjana Zaķe, MD, PhD student, Department of Internal Diseases, RSU, Latvia</p>
15.55 - 16.20	<p>THE ROLE OF SELENIUM IN THYROID AUTOIMMUNITY</p> <p>Ieva Kalere, MD, PhD student, Department of Internal Diseases, RSU, Latvia</p>
16.20 – 16.45	<p>UPDATE IN ENDOCRINE AUTOIMMUNITY</p> <p>Ilze Konrāde, MD, PhD, Assoc. Professor, Department of Internal Diseases, RSU, Latvia</p>

September 30, 2021	
10.00-10.25	AUTOIMMUNITY – FROM DIAGNOSIS TO TREATMENT Howard Amital , Professor, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; Head of the Department of Medicine B and The Zabudowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel
10.25-11.10	ALGORITHM BY IMMUNE PROFILING AND BIOMARKERS TO IDENTIFY INFLAMMATORY, AUTOIMMUNE AND INFECTIOUS DISEASES Marion Schneider , Professor, Ulm University, Germany
11.10 – 11.40	CHARACTERIZATION OF EXTRACELLULAR VESICLES FROM INFLAMMATORY MACROPHAGES STIMULATED BY EXOGENOUS ATP AS A DANGER SIGNAL Christian Scheiber , PhD student, Ulm University, Germany
11.40 – 12.00	MS DISEASE MODIFYING THERAPIES AND COVID-19 (DISEASE OUTCOMES, VACCINATION) Sandra Svilpe MD , Rīga East University Hospital, Latvia
12.00 – 12.15	<i>Break</i>
12.15 – 12.45	CHRONIC INFECTIONS AND LYME CONTRIBUTING TO AUTOIMMUNE DISEASES Kunal Garg , PhD student, Ulm University, Germany
12.45 – 13.15	SERUM NEUROFILAMENTS IN MULTIPLE SCLEROSIS Daina Pastare , MD PhD, Department of Neurology and Neurosurgery, RSU, Latvia
13.15 -13.45	<i>Break</i>
13.45 – 14.15 (30')	ATOPIC DERMATITIS - CURRENT ISSUES, PATHOGENETIC MECHANISMS AND EMERGING THERAPEUTIC PERSPECTIVES Elga Sidhoma , MD, PhD, Department of Dermatology, RSU, Latvia
14.15- 14.45	EARLY SKIN MALIGNANCIES AND THEIR TREATMENT OPTIONS WITH TOPICAL IMMUNOMODULATING AGENTS Alise Balcere , MD, PhD student, Department of Dermatology, RSU, Latvia
14.45 -15.00	<i>Break</i>
15.00 - 15.20	IMMUNE- MEDIATED ATAXIAS Ramona Valante , MD, P. Stradiņš Clinical University Hospital, Latvia
15.20 - 15.45	MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME Santa Rasa-Dzelzkalēja , PhD, Institute of Microbiology and Virology, RSU, Latvia
15.45 - 16.30	TICK - BORNE ENCEPHALITIS AND AUTOIMMUNE OUTCOME – CLINICAL DATA OF LATVIA AND CASE REPORT Angelika Krūmiņa , MD, PhD, Professor, Ilja Drjagunovs , MD, Department of Infectology, RSU, Latvia

List of participants – 29 September 2021

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Anda Vilmane	Institute of Microbiology and Virology, RSU
Andrejs Šķesteris	Laboratory of Biochemistry, RSU
Angelika Krūmiņa	Institute of Microbiology and Virology, RSU
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Asja Lunga	Development and Project Department, RSU
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Daina Pastare	Department of Neurology and Neurosurgery, RSU
Daniel Weißert	Ulm University, Germany
Daria Bortolotti	University of Ferrara, Italy
Dario Di Luca	University of Ferrara, Italy
Dīāna Arāja	Institute of Microbiology and Virology, RSU
Dita Pole	Development and Project Department, RSU
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Ieva Kalere	Department of Internal Diseases, RSU
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Ilze Konrāde	Department of Internal Diseases, RSU
Iļja Drjagunovs	Department of Internal Diseases, RSU
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Iveta Barkāne	ARS Medical centre, Latvia
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Marion Schneider	Ulm University, Germany
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Sandra Svilpe	Rīga East University Hospital, Latvia
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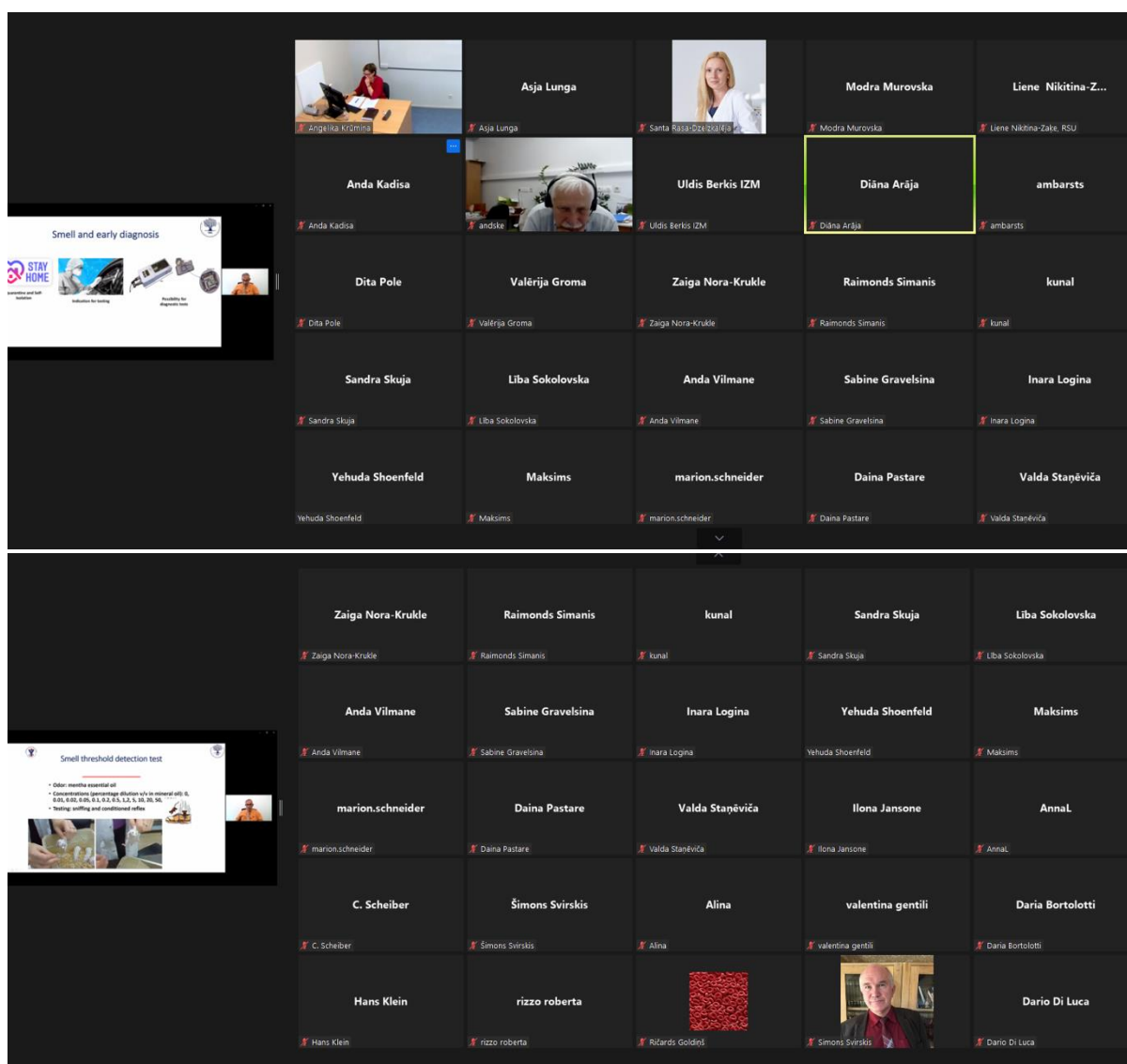
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Svetlana Lakiša	Institute of Occupational Safety and Environmental Health, RSU
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Yehuda Shoenfeld	Tel-Aviv University, Sheba Medical Centre, Israel
Zaiga Nora-Krukle	Institute of Microbiology and Virology, RSU
Zane Straume	Department of Internal Diseases, RSU

List of participants – 30 September 2021

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Ričards Goldiņš	Research Department, RSU
Sabine Gravelisina	Institute of Microbiology and Virology, RSU

Samariešu medicīniskā komisija	Latvian Samaritan Commission
Sandra Skuja	Joint Laboratory of Electron Microscopy, Institute of Anatomy and Anthropology, RSU
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Zaiga Nora-Krūkle	Institute of Microbiology and Virology, RSU

Screenshots from the workshop:



3-day workshop
"NEW TRENDS IN AUTOIMMUNE DISEASES IMMUNOLOGICAL PROFILING"
 27- 29 October, 2021

Contact person – Assoc. Prof. Simona Donina
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Liba Sokolovska	Anda Vilmane	Yehuda Shoenfeld	Maksims
marion.schneider	Valda Stanjevica	C. Scheiber	Alina
valentina gentili	Daria Bortolotti	rizzo roberta	Ilona Jansone
Dario Di Luca	Daina Pastare	Anda Kadisa	Ieva Kalere
Annal	ambarsts	Sabine Gravelisina	Ieva Kalere

Imbalance in autoantibodies titers between women with silicone breast implants and age matched healthy women

Asja Lunga	C. Scheiber	andske	Dita Pole	Sabine Gravelisina
Simons Svirskis	Raimonds Simanis	Sandra Skuja	Simona Donina	Liba Sokolovska
Mihails Tarasovs	Marion Schneider	Anda Kadisa	Daina Pastare	
Sandra Svilpe	Anda Vilmane	Uldis Berkis	Samariestu medicinsk...	

Smell and early diagnosis

Asja Lunga	Modra Murovska	Liene Nikitina-Z...
Anda Kadisa	Uldis Berkis IZM	Diāna Arāja
Dita Pole	Valerija Groma	Zaiga Nora-Krukle
Sandra Skuja	Liba Sokolovska	Anda Vilmane
Yehuda Shoenfeld	Maksims	marion.schneider

3-day workshop
“NEW TRENDS IN AUTOIMMUNE DISEASES IMMUNOLOGICAL PROFILING”
27- 29 October, 2021

Contact person – Assoc. Prof. Simona Donina
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valentina gentili	Daria Bortolotti	rizzo roberta	Simons Svirskis
Dario Di Luca	Daina Pastare	Anda Kadisa	Ilona Jansone
Annal	ambarsts	Sabine Gravelcina	Ieva Kalere

Small threshold detection test

- Color sensitive essential oil
- Concentrations: percentage dilution 1:1 to mineral oil 0, 10%, 50%, 100, 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:20, 1:50
- Testing: sniffing and conditioned reflex

Zaiga Nora-Krukle	Raimonds Simanis	kunal	Sandra Skuja	Liba Sokolovska
Anda Vilmane	Sabine Gravelcina	Inara Logina	Yehuda Shoefeld	Maksims
marion.schneider	Daina Pastare	Valda Stanjevica	Ilona Jansone	Annal
C. Scheiber	Simons Svirskis	Alina	valentina gentili	Daria Bortolotti
Hans Klein	rizzo roberta	Ricards Golds	Simons Svirskis	Dario Di Luca