

GENERAL INFORMATION

1. NAME OF THE CENTER AND LOCATION

National Center of Infectious and Parasitic Diseases
– Centre of Competence - *Fundamental, Translational and Clinical Investigations of Infections and Immunity*
26, Yanko Sakazov boul. 1504, Sofia, Bulgaria

2. TYPE OF THE RESEARCH INFRASTRUCTURE AND/OR SCIENTIFIC EXPERTISE

Identify the type of the RI, equipment/facilities/ specific research, and in particular linked to COVID-19:

NCIPD develops the strategy and policies for management, prevention and elimination of infectious diseases in Bulgaria. This mission translates into intensive research on the etiology, pathogenesis, epidemiology, and immune response to infections. NCIPD comprises the national reference laboratories for diagnosis of various infectious and parasitic diseases, certified since 2003 according to BS ISO EN 17025. NCIPD labs are under constant international laboratory external control provided by international EQA bodies (INSTAND, CDC, WHO). NCIPD is the leading partner in the Center of competence “Fundamental, translational and clinical investigations on infections and immunity” funded through the Operational program Science and education for smart growth (2018 – 2023), aiming to respond to the emerging and re-emerging infections with social impact, and to the ever increasing antimicrobial resistance. NCIPD is well equipped for its reference diagnostic and research activities, including PCR and RT-PCR analyzers, high performance microplate readers, flow cytometers, invert and fluorescent microscopes, Luminex platform for multiplex analyses, cell culture and bio banking facilities.

The equipment of the Center of Competence is currently being upgraded with: two BSL3 labs for handling extremely dangerous viruses and bacteria, an expert virology lab for NGS and molecular epidemiology analysis of viral pathogens; an expert morphology lab equipped for electron, fluorescent and confocal microscopy; an expert microbiology lab for molecular genetics, spectrometry and proteomics (NGS, MALDI-TOF-MS, automated antimicrobial susceptibility testing); an expert immunology lab equipped for flow cytometry, cell sorting and multiplex immunoassay analyses.

KEY WORDS: molecular epidemiology, NGS of pathogenic microorganisms, protective immune response

3. TYPE OF THE RESEARCH

Provide information on the research carried on or planned in regard with COVID-19 and other viruses

1. **Biomarkers of dysregulated and protective immune response in COVID-19 patients.** We are currently conducting multiparameter analysis of the effector and regulatory subsets driving the cellular and humoral immune responses in SARS-CoV-2-positive patients at different terms and with varying severity of infection. Cellular phenotypes will be tested alongside with cytokine expression and SARS-CoV-2- specific antibody titers. Our hypothesis is that a poor outcome results from an early and predictable dysregulation of the balanced differentiation of Th1/Th2/Th17 and Treg subsets, leading to inefficient antiviral cytotoxicity and overproduction of proinflammatory cytokines. Our aim is to define the “footprint” of protective vs. inefficient immunity, that will serve monitoring, prognosis and testing of vaccinal and immunomodulatory prototypes. In parallel we are preparing a stock of isolated mononuclear cells and sera samples that could be used in further projects for antigen characterization, pre-clinical validation, and clinical development of vaccines or therapeutic preparations
2. **Phylogenetic analysis of COVID-19 lineages circulating in Bulgaria by means of shotgun NGS analysis.** Various samples from symptomatic and asymptomatic patients will be studied in order to associate potential mutations related to pathogenesis.
3. **Development of rapid and cost-effective diagnostic assays** based on Loop-mediated isothermal amplification (LAMP) with direct application without the need for prior RNA extraction and/or minimal sample processing.

4. WEBSITE

Provide the internet address:

<https://www.ncipd.org/index.php?lang=bg>
www.ncipd.org

5. BACKGROUND, PUBLICATIONS AND OPEN DATA REPOSITORY

leading research team AND Scientific publications of the research group on the topics of related to coronaviruses research results;
link to open data repository

Research teams:

1. Prof. Maria Nikolova, MD, Dsc
Head, Reference laboratory of Immunology
Head, Immunology and Allergy Department
National Center of Infectious and Parasitic Diseases
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Members:

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Assist. prof. Yana Todorova, PhD, y_todorova@abv.bg

2. and 3. Assoc. Prof. Ivan Ivanov, PhD
Head, Reference laboratory for control and monitoring of antibiotics resistance; National Center of Infectious and Parasitic Diseases
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Members: Assoc. Prof .Victoria Levterova

Assoc. prof. Neli Korsun

Assoc. prof Ivaylo Alexiev

Assist. Prof. Ivan Simeonovski

- Elevated Labile Iron Levels in CD4 and CD8 T Cells From HIV Positive Individuals With Undetectable Viral Load R Emilova, V Manolov, Y Todorova, N Yancheva, I Alexiev, M Nikolova, *AIDS Research and Human Retroviruses*, DOI: 10.1089/AID.2020.0010
- T cell effector and regulatory subsets, differentiating between active and latent MTB infection Y. Todorova, R Emilova, V Milanov, L Eneva, E Bachijska, J Atanasova, A Bajkova, M Nikolova., *Probl Infect Parasit Dis*, 2019, vol. 47 (1): 30-38
- Nikolova M, Markova R, Drenska R, Muhtarova M, Todorova Y, Dimitrov V, Taskov H, Saltini C, Amicosante M Antigen-specific CD4- and CD8-positive signatures in different phases of Mycobacterium tuberculosis infection. *Diagn Microbiol Infect Dis*. 2013 Mar; 75(3):277-81. 2012.11.023.
- Nikolova, M., Carriere, M., Jenabian, M.-A., Limou, S., Younas, M., Kök, A., Huë, S., Seddiki, N., Hulin, A., Delaneau, O., Schuitemaker, H., Herbeck, J.T., Mullins, J.I., Muhtarova, M., Bensussan, A., Zagury, J.-F., Lelievre, J.-D., Lévy, Y. CD39/adenosine pathway is involved in AIDS progression (2011) *PLoS Pathogens*, 7 (7), art. no. e1002110
- Nikolova, M., Lelievre, J.-D., Carriere, M., Bensussan, A., Lévy, Y. Regulatory T cells differentially modulate the maturation and apoptosis of human CD8+ T-cell subsets (2009) *Blood*, 113 (19), pp. 4556-4565.
- First clinical cases of NDM-1-producing Klebsiella pneumoniae from two hospitals in Bulgaria.
Todorova B, Sabtcheva S, Ivanov IN, Lesseva M, Chalashkanov T, Ioneva M, Bachvarova A, Dobрева E, Kantardjiev T. *J Infect Chemother*. 2016 Dec;22(12):837-840.
- Detection and characterization of OXA-48-producing Klebsiella pneumoniae originated in Bulgaria. Sabtcheva S, Ivanov IN, Todorova B, Simeonov Y, Dobрева E, Ivanova K, Velinov T, Kantardjiev T. *J Chemother*. 2016 Oct;28(5):450-3. .
- Two-Year Monitoring of Water Samples from Dam of Iskar and the Black Sea, Bulgaria, by Molecular Analysis: Focus on Mycobacterium spp. Panaiotov S, Simeonovski I, Levterova V, Karamfilov V, Brankova N, Tankova K, Campbell K, Jacob P, Helmi K, Boots B, D'Ugo E, Marcheggiani S, Mancini L, Breitenbach U, Mielke E, Kantardjiev T. *Int J Environ Res Public Health*. 2015 Jun 30;12(7):7430-43.
- Predominance of influenza B/Yamagata lineage viruses in Bulgaria during the 2017/2018 season. Korsun NS, Angelova SG, Trifonova IT, Georgieva IL, Tzotcheva IS, Mileva SD, Voleva SE, Kurchatova AM, Perenovska PI. *Epidemiol Infect*. 2019 Jan;147: e76.
- Origin and Spread of HIV-1 Subtype B Among Heterosexual Individuals in Bulgaria. Alexiev I, Lo Presti A, Dimitrova R, et al. *AIDS Res Hum Retroviruses*. 2018 Mar;34(3):244-253. Jan 23.
- Antigenic and genetic characterization of influenza viruses circulating in

Bulgaria during the 2015/2016 season. Korsun N, Angelova S, Gregory V, Daniels R, Georgieva I, McCauley J. *Infect Genet Evol.* 2017 Apr;49:241-250.

- Origin and spread of HIV-1 in persons who inject drugs in Bulgaria. Alexiev I, Shankar A, Dimitrova R, et al. *Infect Genet Evol.* 2016 Dec; 46:269-278.

6. COORDINATOR

Full name of the coordinator organization;

National Center of Infectious and Parasitic Diseases

– Centre of Competence - Fundamental, Translational and Clinical Investigations of Infections and Infectious Immunology

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Contact person

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Director of NCIPD

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7. POSSIBLE PARTNERS

Indicate the partner organizations

Full name of the partner

Military Medical Academy

Department of Infectious Diseases

Contact person;

Ass. Professor Georgi Popov, MD, PhD

Head, Department of Infectious Diseases

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Full name of the partner

Institute of Microbiology Stephan Angelov

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Contact person;

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Full name of the partner

University Tor Vergata

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Contact person;

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University of Rome "Tor Vergata" and Proxagen Ltd: SME - development and implementation of prototypes for human and animal vaccines and diagnostic systems;

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Full name of the partner

VRI - Vaccine Research Institute
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8. IMPLEMENTED AND RUNNING PROJECTS

Projects related to
virology, vaccines,
infection diseases ...

1. Science and Education for Smart growth Operational Programme grant - Creation and Development of Centers of Competence - „Fundamental, Translational and Clinical Investigations of Infections and Infectious Immunology“; BG05M2OP001-1.002-0001; 2018–2023.
2. Regulatory Mechanisms of Protective T-cell Immune Response to Mycobacterium tuberculosis, DN 1/13 2017 0 2021; Bulgarian Science Fund; project coordinator *M. Nikolova*
3. Genomic characteristics responsible for drug resistance (rezistome) and virulence (virulom) in extensive and pan-resistant *Pseudomonas* spp. H23/24 Bulgarian Science Fund; 2018 - 2022, project coordinator *I. Ivanov*
4. Crimean Congo hemorrhagic fever: Modern Approaches to Diagnostics, Surveillance, Prevention, Therapy and Preparedness. Funded by EU 7 Frame. Call FP7-HEALTH-2010 (2010-2013), PI: Ali Mirazimi, project No. 260427
5. ASSET_CA_2013-11-15- 612236/ 15.11.2013 Action Plan on SiS Related Issues in Epidemics and Total Pandemics 2013 - project coordinator *I. Hristova*
6. FB7-KBBE-2010-4/ 01.03.2011 Universal microarrays for the evaluation of fresh-water quality based on detection of pathogens and their toxins 2010 – 2016
7. F3-2008-202145/ 31.01.2008 A new platform for fast molecular detection of MDR and XDR resistant strains of *M. tuberculosis* and of drug resistant malaria (2008 – 2014)
8. T-regulatory cells and CD8 T cell immune responses in the settings of HIV infection; possible role of PD1/PDL1 and CD39/ATP signaling pathways. in collaboration with INSERM U841, Prof. Yves Levy, Program for Franco-Bulgarian scientific collaboration “RILA”, 2009 – 2011, project coordinator *M. Nikolova*
9. F5-2007-200481/ 01.08.2008 Design of a vaccine to immunize neonates against GBS infections through a durable maternal immune response 2008- 2014
10. European Influenza Surveillance Network (EISN), European Society for translational Antiviral Research (ESAR); subject: molecular epidemiology of drug-resistant viruses in Europe