The Stephan Angeloff INSTITUTE OF MICROBIOLOGY, Bulgarian Academy of Sciences (BAS) is a national research center in microbiological sciences

Director: Professor Hristo Najdenski, DVM, DSc - hnajdenski@abv.bg

Strategic lines have been established:

- INVESTIGATIONS on problems implicated in public health and biotechnology
- TEACHING activities and training of PhD students

The Institute of Microbiology was founded on March 7, 1947. total of over 30 projects are funded by foreign institutions (FP7 of the EC, NATO grants, UNESCO, Institute Pasteur, the French Government, the Swiss Government, and by companies abroad), and National Science Research Fund at the Ministry of Education and Science, Bulgaria.

The educational activities:

- Doctoral studies (35 PhD students within the last five years)
- Training courses for young scientists from the Balkan countries at the Atelier Pasteur

INTERNATIONAL COLLABORATION

Collaboration between the IMSA and Saint-Petersburg Institute Pasteur and Institute Pasteur of Guadeloupe (**drug-resistant TB**)

Institute Pasteur Paris (human **papillomaviruses**, genetics of primary **HBV/HCV-induced liver carcinoma**)

German Center of Cancer Research (DKFZ, Heidelberg) (**oncolytic viruses**)

University of Leipzig and the Technical University of Dresden (plant cell cultures and **biotechnologies**)

University of Viterbo and University of Pavia (new **enzymes** of **Antarctic** microorganisms)

University of Strathclyde, Glasgow (**biotechnologies** of eukaryotic microorganisms)

University of Naples (enzymes from thermopile **bacteria**)

Institute of Agricultural Sciences and Fishery, Ghent (control on **food products**)

1- Department OF General Microbiology - Head: Dr Zlatka Alexieva, PhD zlatkama@microbio.bas.bg

1-1 Section of morphology of microorganism and electron microscopy

Head: Dr Stoyanka Stoitzova, e-mail: stoitsova_microbiobas@yahoo.com

Research Area

- Fine structure of pathogenic and non-pathogenic microbial species.
- Cytochemical and immunocytochemical localization of enzymes and biopolymers.
- Immobilization on various matrices and nanomaterials, and under the action of bio surfactants, signal molecules and physicochemical factors.
- Cell-to-cell antigen variations.
- Biofilms: structure, and activation or inhibition of biofilm growth. Development and modulation by natural products

1-2 Section of microbial Genetics

Head: Zlatka Alexieva, PhD - e-mail: zlatkama@microbio.bas.bg

- **The main research** is focused on the **genetic analysis and regulation of genes** in microorganisms
- Molecular taxonomic characterization of lactobacilli isolated from Bulgarian dairy products
- Characterization of probiotic potential of Lactic acid bacteria,
- Studying the molecular mechanisms of resistance to industrial stress
- Isolation and molecular genetic analysis of vaginal lactobacilli
- Cloning and sequence analysis of the genes involved in the biosynthesis of spectinomycin in *Streptomyces flavopersicus*
- Construction of yeast strains *Ogataea polymorpha* for the expression of heterologous genes
- capable of efficient degradation of toxicaromatic and aliphatic compounds
- Obtaining of DNA sequences to study the biodegradation potential of microbial strains in industrial contaminated water and soils
- Investigation on the ability of microorganisms for biodegradation of monoaromatic and polyromantic pollutants of the environment.

1-3 Section of Microbial Biochemistry

Head: Dr Evgenia Vasileva-Tonkova, PhD - e-mail:evaston@yahoo.com

- Studies on enzymes: secretion, isolation, characterization, properties.
  - **Neuraminidases** – studies on the role in infection.
- Biological active substances of microbial and synthetic origin- antimicrobial activity, mechanisms of action.
- Microbial surfactants: biosynthesis, physico-chemical properties, applications, effects on microbial cell surface.

- Characterization and biosynthetic potential of new mesophilic and psychrophilic/psychrotolerant bacteria and yeasts.

2- Department of applied microbiology - Head: Professor Atanas Pavlov, DSc - e-mail: at_pavlov@yahoo.com

2-1 LABORATORY OF MICROBIAL BIOSYNTHESIS AND ECOLOGY

Head: Assoc. Professor Kolishka Tzekova, PhD - e-mail:ktsekova@microbio.bas.bg

- Physiology, biochemistry, biosynthesis and identification of primary and secondary metabolites of **Actinomycetes and filamentous fungi**.
  - taxonomy, physiology, biochemistry and biosynthesis of enzymes, antibiotics and stimulators from Actinomycetes;
  - Isolation, purification and structure of biologically active substances of filamentous fungi.
  - Optimization of conditions for production of extracellular hydrolytic enzymes by free and immobilized cells.
- Investigation on **physiological response of microorganisms** to different pollution: heavy metals, phenol, oil products
- **Bioremediation** of different **xenobiotic** by free and immobilized cells.
- The changes in the structure and function of microbial communities in river and marine ecosystems in presence of **xenobiotic**.
- **Detoxification** of aquatic ecosystems.

Most Important Achievements:

- A method for production of extra cellular α-galactosidase
- A detailed "know-how" for production of L-lysine and a Lab biotechnology for production of L-valine were developed.
- An alkaline hydrolysate from animal wastes: influence on of poor soils and the possibilities for application as organic fertilizer.
- The strain Streptomyces sp. producer of antibiotic complex, was identified by hemotaxonomic and genetic methods as Streptomyces iakurus DSM 41873.
- Microbial associations degrading phenol and oil products were selected.
- An immobilized system of **organic polymer with fungal biomass possessing potential for heavy metal** ions removing is created.

Ongoing projects

- "Microbial synthesis of alkaloids and amino acids" cooperation BAS and RTM " Recourses + Technologies – Management", Germany
- "Carrying out of preliminary test experiments" between BAS and FAD "Plemzavod-Jubileinii", Russian Federation.
- "Optimization of fermentation processes for amino acid production" between BAS and RTM " Recourses + Technologies – Management", Germany
- "Anaerobic biodegradation of lignocellulosic wastes in order to produce bio gas and utilization of carbon dioxide in it by using microalgae"

- „Cultivation of micro-algae in innovative photo-bioreactor for carbon dioxide sequestration from industrial waste gases from different sources and synthesis of high value products”

2-2 LABORATORY OF EXTREMOPHILIC BACTERIA

Head: Dr Margarita Kambourova, PhD - e-mail: margikam@microbio.bas.bg

- Biodiversity of extremophilic bacteria.
- Biosynthetic capacity of extremophilic microorganisms to synthesize biotechnologically valuable enzymes.
- Purification and characterization of thermostable enzymes.
- Biosynthesis of exopolysaccharides from extremophilic microorganisms – thermophiles and halophiles.
- Work on EPSs from halophiles and extremophilic bacteria.

Resent projects:

- Metagenomics approach identification and biosynthesis of acidic thermostable **α-amylase** from thermophilic microorganisms.
- Biosynthesis of exopolysaccharides from extremophilic microorganisms.
- Biodiversity of halophilic microorganisms, isolated salt niches and their potential for exopolysaccharide synthesis.

2-3 LABORATORY OF APPLIED BIOTECHNOLOGIES

Head: Professor Atanas Pavlov, DSc - e-mail: at_pavlov@yahoo.com

- Works on microbial and plant biotechnologies: Production of biologically active substances for medicine, pharmaceutical and cosmetic industries; starter cultures and additives for the food industry.
    - Microbial biotechnologies: physiology and biochemistry of yeasts and lactic acid bacteria for synthesis of biologically active substances.
    - Plant biotechnologies: establishment of plant in vitro culture and application in the biosynthesis of low molecular weight biologically active substances, enzymes and polysaccharides.

Last ten years international projects:

- Biomonitoring in plant biotechnology through flow cytometry. Sächsiches Staatsministerium für Wissenschaft, Germany**.**
- Investigation of plant in vitro systems of Salvia species with different ploidy levels. Program PPP of DAAD, Germany.
- Bioproduction of pharmaceutically important iridoids. Program, Marie Curie Intra European Fellowships, 7FP of EU.
- Rational platform for halogenation of high-value phenylethanoid glycosides from plant root culture. Program PPP of DAAD, Germany.

2-4 Work group “MATHEMATICAL MODELLING AND COMPUTER SCIENCES”

Head: Dr Ivan Simeonov, PhD - mail: issim@microbio.bas.bg

- Mathematical, neural and hybrid modelling, state and parameter estimation, optimization and control of microbiological processes and biotechnological systems.
    - Anaerobic digestion of organic wastes from agriculture, waste water treatment plants, food industry.
    - The microbial composition, metabolite products and biochemical mechanisms of substrate degradation.

Current Projects

- New Ecotechnologies for biodegradation of organic waste with hydrogen and methane production.
- Study of anaerobic biodegradation possibilities for organic wastes. IM-BAS+IMBP-Moscow, Russia + University of Lille, France.

3- Department of Infectious Microbiology -

Head: Professor Hristo Najdenski, DVM, DSc - hnajdenski@abv.bg

- Characterization of bacterial-host interactions in socially important **zoonosis** and others **emerging** infections
- molecular analysis of Mycobacterium tuberculosis : multidrug resistant strains and monitoring the burden and transmission
- in vitro determination of antibacterial and antifungal activities of substances with organic and non-organic origin
- Photobiology and photodynamic inactivation of bacterial pathogens.

3-1 LABORATORY OF ZOONOZES AND BACTERIAL VIRULENCE

Head: Professor Hristo Najdenski, DVM, DSc

Main Research topics

- Epidemiology, epizootology, and prevention of yersiniosis.
- Epizootology and prevention of mycobacterial infections in domestic animals and birds.
- Detection, enumeration and typing of socially important food-borne zoonoses in products of animal origin.
- Detection of American foulbrood agent in honey, honeybee brood, and worker bee.
- Bacterial virulence factors and immune pathogenesis of genetically designed live vaccinal vectors.
- Antimicrobial susceptibility testing of food pathogens, enteropathogens and pathogenic fungi.
- Antifungal and antibacterial effect of natural products of plant, microbial and algal origin.
- Toxicological profiling and cytotoxic potential of bacterial products, natural products with high antimicrobial activity.
- Molecular epidemiology, phylogeny, evolution and drug resistance of Mycobacterium tuberculosis clinical strains in Bulgaria.
- Search of new effective anti-tubercular drugs: design, synthesis and testing for anti-mycobacterial activity.

Current Projects

- Detection, identification and epidemiological analysis of Yersinia species in pig meat and tonsils (IMSA-ILVO, Belgium)
- Development of vaccine against Chlamydia trachomatis (bilateral project IMSA – Medical University, Vienna, Austria)

- Translational research in hematology, in vitro models for chemo sensitivity testing by patients with multiple myeloma
- in vitro laboratory for cytotoxicity and related cell signaling research grant from the Alexander von Humboldt Foundation
- "Biotechnological & green approach for effective utilization of waste plant biomass for preparation of compost and soil improvers"
- Identification and typing of pathogenic Escherichia coli from pathological material from ruminants.
- New eco-technologies for biodegradation of organic waste with production of hydrogen and methane.

3-2 LABORATORY GENETICS AND DRUG RESISTANCE OF MYCOBACTERIA

Head: Dr Nadya Markova, MD, PhD - e-mail: nadya.markova@gmail.com; markn@bas.bg

- Mycobacteriosis, atypical and cell wall deficient mycobacteria (L-forms):
  - Basic research on pathogenesis of mycobacteriosis and latent mycobacterial infections.
  - Development of molecular biological approaches for detection and identification of mycobacterial L-forms.
  - Molecular mechanisms of drug resistance and drug tolerance of mycobacterial L-forms to anti-mycobacterial agents.
  - Evaluation of drug action against mycobacteria and L-forms.

3-3 LABORATORY OF ANTIMICROBIAL AGENTS

Head: Dr Vesselin Kussovski, PhD - e-mail: veselinkussovski@yahoo.com

- Antimicrobial photodynamic efficiency of novel phthalocyanine complexes and cationic porphyrins towards dental pathogenic bacteria.
- Antifungal and antibacterial effect of natural products of plant, microbial and algal origin, as well as screening of newly synthesized compounds

Current Project

- Water-soluble Phthalocyanines for Fluorescence Diagnosis and Photodynamic Therapy. Joint Research Project TUBITAK – BAS, Gebze Institute of Technology, Turkey

4- DEPARTMENT OF VIROLOGY - Head: Dr Lyubka Doumanova-Iazadjieva, PhD - doumanova@microbio.bas.bg

- Viral replication inhibitors - ligands of viral proteins: mode of action, resistance, combination effects of viral inhibitors
- Combined action of viral replication inhibitors and biological response modifiers
- Search for new viral inhibitors of synthetic and natural origin
- Antiviral microbicides
- Viral proteins
- Human papillomaviruses
- Antiviral drug-resistance

- Viruses – diabetes
- Oncolytic effects of parvoviruses

Most Important Achievements

- Discovery of new original antiviral substances effective in the treatment of viral infections:
    - **Guanidine derivative**: inhibiting replication of adenoviruses. It's first known anti adenoviral chemotherapeutic agent.
    - **Cyclic urea derivatives**, inhibiting selectively replication of influenza and toga viruses.
    - **Dipyridamole** used for prevention of flu and other acute viral respiratory infections.
- Development approaches for selection of synergistic combinations of antimetabolites effective against herpesviruses
- Clearing-up of the mode of antiviral action of mopyridone on influenza A virus replication.
- Discovery and characterization antiviral effect of cycluridine towards flavivirus infections, the first chemotherapeutic agent efficacious in the mucosal disease-virus diarrhea in cattle.
- Development of the concept for low-molecular weight interferon inducers as inhibitors of the cyclic AMP phosphodiesterase.
- Clearing-up of the drug-resistance in enterovirus replication inhibitors interacting with the viral capsid protein VP1.
- Establishment of the synergistic combination effect of cidofovir and idoxuridine against vaccinia virus replication.
- Discovery of oxoglaucine: a highly effective inhibitor of enterovirus replication.
- Establishment of the anti-influenza virus effects of novel protease inhibitors from Streptomyces.
- New proves on the diabetogenic role of neurotropic viruses.

Laboratories:

1- Experimental **Chemotherapy of entroviral infections** - Head: Dr Ivanka Nikolova, PhD
2- Experimental **Chemotherapy of influenza** - Head: Dr Lora Simeonova, PhD
3- Laboratory **oncolytic virous** - Head: Dr Assya Angelova, PhD
4- Laboratory **viral proteins** - Head: Dr Lyubka Doumanova-Iazadjieva, PhD

5- DEPARTMENT OF IMMUNOLOGY - Head: Professor Nina Ivanovska, DSc - nina@microbio.bas.bg

- Constructed chimeric molecules **monoclonal antibodies** to suppress selectively the activity of targeted autoreactive B and T-lymphocytes and to change the natural course of an autoimmune disease.
- **Constructed DNA vaccines** encoding a T and B cell epitope-containing influenza hemagglutinin peptide and a scFv antibody fragment.
- The role of properdin, in experimental models of sepsis and arthritis.
- Contributed to osteoimmunology research by determining on a molecular level the manner in which inflammation impairs bone formation and the extent to which signaling pathways are altered as a consequence.
    - Current work is focused on application of glucosamine as a potential ant arthritic agent.

5-1 LABORATORY OF INFECTIOUS IMMUNOLOGY AND INFLAMMATION

Head: Professor Nina Ivanovska, DSc

Main Research topics:

- Bacterial and Fungal infections, Arthritis, Osteoarthritis, Complement System

Projects

- Application of tyrosine kinase inhibitor tyrphostin AG-490 in a model of collagenase-induced osteoarthritis.
- Mechanisms of anti-inflammatory action of tyrphostin AG490.
- Nuclear factor kappa-b (RANKL)-dependent action of glucosamine.

5-2 LABORATORY OF EXPERIMENTAL IMMUNOLOGY

Head: Dr Andrey Tchorbanov, PhD

- Autoimmunity
- New generation of vaccines and immunoglobulin preparations
- Acute and chronic inflammation

Projects

- "New approach for selective suppression of autoreactive B cells by a chimeric anti-CD35 antibody"
- "Generation of gene-engineered chimeric DNA molecules by recombinant technologies for specific therapy of autoimmune diseases"
- "Creation of engineered chimeric molecules by protein nano-technology for therapy of autoimmune diseases"
- "Genetically engineered viral DNA vaccines"
- "Suppression of allergen-specific B lymphocytes in humanized SCID mice using Chimeric protein-engineered antibodies"
- "Biologic response of neoplastic and auto-immune B-cells to chimeric protein-engineered antibodies: flow cytometry analysis of apoptosis using novel cyanine nucleic acid dyes"
- "DNA vaccines: Viral Antigen Targeting by Genetically Engineered Chimeric Molecules"
- "Antitumor activity of Gastropodan hemocyanins"
- "Functional elimination of autoreactive T cells by antibody therapy in murine and humanized SCID models of Systemic lupus erythematosus and Multiple sclerosis "

5-3 LABORATORY OF EXPERIMENTAL IMMUNOTHERAPY

Head: Dr Anastas Pashov, PhD - e-mail: a_pashov@microbio.bas.bg

- Novel immunotherapeutic based on intravenous immunoglobulins
- Immunotherapy of sepsis,
- Immunotherapy of inflammatory and degenerative tissue damage,

- Immunogenicity of biopharmaceuticals,
- Development of biomarkers based on system analysis of the antibody repertoire

Projects

- Design of modified immunoglobuin with induced polyspecificity for passive immunotherapy of sepsis,
- Therapeutic potential of modified pooled IgM and IgG in experimental SIRS and sepsis
- Translational study on the antigen presenting properties of human vs mouse B cell subpopulations
- Effective training of students and career development of post-docs and young researchers priority microbiology".
- expression in properdin-deficient mice is associated with better outcome from collagen-antibody-induced arthritis
- The role of neutrophils and NK cells in the development of collagenase-induced osteoarthritis,

6- Section of MYCOLOGY - Head: Dr Ekaterina Krumova, PhD - e-mail: ekrumova@abv.bg

- Taxonomic identification of fungal species;
- Fungal cell response against different type of stresses + evaluation of oxidative stress biomarkers + antioxidant enzyme defence;
- Fungal cell factories for production of valuable biological-active compounds by free and immobilized cultures; cold-active enzymes; regulatory mechanisms in the biosynthesis; purification and characterization of enzymes;
- Fungal biodegradation of natural and synthetic polymers + instructions for preservation and elimination of fungi; mechanism of fungicide.

Current Research

1. Fungal diversity
2. Oxidative stress (OS):
    - stress biomarkers
    - antioxidant enzyme defence
    - subcellular localization of SOD isoenzymes
    - changes in activities of key enzymes from basic metabolite pathways
3. Relationship between OS and other types of stresses
    - Cu-induced stress.
    - Heat-shock.
    - Metabolite adaptation to cold temperatures
    - Stress of immobilization.
4. Fungi as cell factories for production of valuable biological-active compounds
    - Produce biological-active compounds such as enzymes and alkaloids.
    - High effective technology for biosynthesis of naturally glycosylated Cu/Zn-SOD
    - Investigations of the biosynthesis and regulation of activity of valuable cold-active enzymes in psychrophilic and psychrotrophic fungi.
5. Fungal biodegradation of natural and synthetic polymers

Projects

- Granted by International Organizations
- Superoxide dismutase by Aspergillus niger: heat shock-induced biosynthesis and structural characterization. Padua, Italy + NATO.

- Bilateral projects
    - Cold-adaptation of Antarctic fungi and their application (University of Pavia, Italy)
    - Biotechnological production of cold-active enzymes by fungi (University of Pavia, Italy)

- EBR projects
    - Study of the physiological, biochemical and ecological characteristics of micromycetes resistant to heavy metal stress. Collaborator: V. Grishko, Ukrainian Academy of Sciences.
    - Efficacy of antimicrobial substances produced by streptomyces in modifying polymers used in conservation of paintings in some ancient egyptian tombs. collaborator: M. Farrag, PhD, Zagazig University, Faculty of Science, Botany Department, Egypt

7- Laboratory Center PASTEUR - Head: Dr Peter Grozdanov, PhD - e-mail: grozdanov@microbio.bas.bg

Main Topics

- Training Courses for Young Scientists

First International Training Course:

- "Molecular Biology Applied to the Detection and the Typing of Microorganisms"
    - Lecturers: Prof. Dr. P. Boiron (Lyon), Dr. J.-C. Manuguerra (Paris), Dr. N. Tordo (Paris), Dr. M. Damian (Bucharest) and Dr. M. Straut (Bucharest) 12 participants from Bulgaria, Romania and Greece

Second International Course:

- "Molecular Methods for Identification and Typing of Viruses and Mycetes"
    - Lecturers: Prof. Dr. P. Boiron (Lyon), Prof. Dr. M. Angelova (Sofia), Dr. J.-C. Manuguerra (Paris) and Dr. N. Tordo (Paris) 10 participants from Bulgaria, Romania and Republic of Macedonia

Third International Course:

- "Methods for DNA Finger-Printing and Genotyping of Drug-Resistant Strains of Mycobacterium tuberculosis"
    - Lecturers: Prof. Olga Narvskaya (St.-Petersbourg) and Dr. Igor Mokrousov (St. Petersbourg) 10 participants from Bulgaria, Romania and Republic of Macedonia