New Trends in Infectious Diseases
Nouvelles perspectives dans le domaine des maladies infectieuses

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The **EU-CIS Seminar – New Trends in Infectious Diseases**, Lyon, France, 26 – 28 November 2008, is organized in the frame of the French Presidency of the European Union by the "Institut National de la Santé et de la Recherche Médicale (Inserm), the International Science and Technology Center (ISTC) and the Science and Technology Center in Ukraine (STCU) and with the support of the European Commission.

Theme of the Seminar:

In 1877, Louis Pasteur and Robert Koch discovered the growth inhibiting effects of *Penicillium sp* on *Bacillus anthracis*. However, it took more than 30 years before modern research on antibiotic therapy began by Paul Ehrlich and his contemporaries. It took another 20 years before Alexander Fleming discovered Penicillin, and only by the late 1930's did antibiotics become commercially available. Since these initial discoveries, a broad range of antibiotics has been developed and currently they are commonly used for the treatment of bacterial infections in humans and animals. As a result of these discoveries modern medicine has made great progress in treating and preventing infectious outbreaks.

However, during the last few decades only a small number of new antibiotics have been released onto the market, while at the same time more and more bacterial infections have emerged that are not only drug-resistant (DR), but also multi-drug resistant (MDR). Emerging microbial resistance is of great concern to the medical community, because drugs that are available to treat infectious diseases are becoming less effective while only few drugs are being released that can address drug-resistance. Additionally, the world population has increased 4-5 fold since the first discovery by Pasteur and Koch, resulting in many areas in the world with high population densities that are highly susceptible to pandemic outbreaks.

Therefore, it is important that:

- Greater diligence is given to **disease surveillance**, in order to better understand what new kinds of diseases are emerging (Session 1), and to deal with possible outbreaks early-on;
- **Drug resistance in infectious diseases** is studied in greater detail, in order to better understand how to anticipate and circumvent or adjust to drug resistance in infectious diseases (Session 2)
- **Characterization and improved diagnostics of infectious diseases** are improved to better understand the mechanism of action in humans and animals and to obtain quick, cheap and easy to use diagnostics that will assist medical and health care professionals in their diagnosis of patients accurately and quickly (Session 3)
- **New antimicrobials** are developed, designed and validated, which are based on different mechanisms of action compared to existing treatments in order to circumvent drug resistance (Session 4)
- **Zoonotic diseases** are studied, in order to better understand and prevent the transmission of infectious diseases from animals to humans (Session 5)

Objectives of the Seminar:

- To exhibit the capabilities, existing treatments and developments of science in the CIS in the field of drug discovery, in order to stimulate partnering/commercial activities with companies
- To enhance the exchange of information between European and CIS scientists in order to address new emerging diseases. This is of essential importance given that many highly infectious diseases are endemic in various CIS countries (especially Central Asia)

To stimulate new ideas by bringing scientists from different research backgrounds and cultures to generate new concepts to tackle the issue of drug-resistance in infectious diseases

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SESSION 1 - Public Health, Epidemiology, and Disease Surveillance

SURVEILLANCE of INFECTIOUS DISEASES in FRANCE

Anne Gallay, Jean-Claude Desenclos, Institut de Veille Sanitaire, Saint-Maurice, France

Surveillance is a continuous and systematic process of collection, analysis and diffusion of health data to all those who contributed to their collection and all those who need to know in order to take action. Surveillance activities are targeted in priority to health problems for which effective prevention or control measures are available. Surveillance objectives include the following of trends and changes in diseases characteristics, evaluation of public health actions and early detection of infectious diseases threats and epidemic and their investigation. The data produced by surveillance systems allow prioritizing public health actions and defining the objectives of infectious diseases control or prevention. Surveillance of infectious diseases relies on a large number of partners assembled in a public health network in which clinicians and microbiologists are at the front line. In France, surveillance of infectious diseases is done under the auspices of the Institut de Veille Sanitaire (InVS, National public health surveillance Institute) which missions are public health surveillance of the population; detect emerging public health threats to alert health authorities, and to identify the determinants of health status changes. Decision makers are the main priority target of the InVS to advice on management, control and prevention issues that is under the responsibility of the Ministry of Health. The mandate of the InVS includes all risks for public health: infectious, environmental, occupational, chronic diseases, injury, and mental health. The InVS is the national competent body for European surveillance of Infectious diseases done by the European Centre for Disease Control and Prevention (ECDC). Surveillance of infectious diseases is based on diseases mandatory notification, national reference centres, voluntary health professional networks, syndromic surveillance, repeated surveys and use of databases such as mortality data bases, hospital discharges... Collaboration with European national surveillance institutes through Surveillance and Early warning systems developed under the ECDC, along with international watch of emerging risks complement the national surveillance activities to take into account the global dimension of infectious diseases spread. The InVS has also a strong interaction with applied public health research on infectious diseases.

ORGANIZATION OF SURVEILLANCE AND LABORATORY DIAGNOSTICS OF INFECTIOUS DISEASES IN THE RUSSIAN FEDERATION

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To organize monitoring of pathogens accountable for infectious and parasitic diseases, as well as to implement “International medical- and-sanitary rules” (2005) on the territory of Russia, a multi-level system of laboratory diagnostics involving a number of diagnostic centers has been established.

Regional centers for monitoring of pathogens (II-IV class of pathogenicity; according to Russian classification) are set up on the basis of centers of hygiene and epidemiology in different subjects of the Russian Federation. Centers of surveillance of causative agents of I-II class pathogenicity are structured into anti-plaque institutions. They focus on research in the field of virology, parasitology, serology and molecular biology to identify etiological factors of infectious and parasitic diseases.

Centers of indication and diagnosis of dangerous infectious diseases are set up in Federal districts of the Russian Federation on the basis of anti-plaque institutions structured into Rospotrebnadzor, as well as of specialized science institutions. The main goal of such centers is to indicate and diagnose dangerous infectious diseases of bacterial and viral nature to identify the etiological factor in order to prevent and eliminate potential emergent situation consequences. Centers use methods of express diagnostics (MFA, bacterioscopy) and speed diagnostics (PCR, IFA, serologic reactions) and are in a position of making the entire bacteriological analysis.

There are also reference-centers structured into different science institutions. They are intended for laboratory diagnostics and monitoring of pathogens causing infectious and parasitic diseases to provide advisory and practical assistance for health care bodies and institutions. They identify and study pathogens of infectious and parasitic diseases, including atypical property cultures and newly identified agents.

National verification centers are also available. They are structured into significant epidemiological and microbiological research institutions and are responsible for verification of results from diagnostics and identification of infectious diseases with unknown etiology and severe clinical symptoms. They also conduct molecular- epidemiologic research and study viral, bacteriological, molecular –biological, serologic and immunochemical properties of especially dangerous pathogens.

UKRAINE: STRENGTHENING OF THE EPIDEMIOLOGICAL SURVEILLANCE SYSTEM TROUGH NATIONAL PROGRAMMES AND INTERNATIONAL COOPERATION

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Ukraine – transit country located in the Central Europe. Territory – 603700 sq.km. Population – 46,5 mln. Independent sine 1991.
Geopolitical position on the transcontinental traces shows possible penetration and distribution of the Biological Pathogenic Agents (BPA) in the country.

Ukraine support counter epidemic protection of the territory and population through National Programs. These reflect in the Constitution, legislation administrative documents. In practice – under supervision of the existed biological control system net of scientific and practical, state and local, based on SES and territorial services including Indication and Identification Centers. State cooperates with the International organizations in Global Biosafety and Biosecurity System creation. In frames of “Ukraine-EU” Programme on Counter Bioterrorism, permanent data exchange is in progress as well as sharing with infectious diseases control experience. By the requests of the WHO Ukraine informs about different agents circulation. Country support International Sanitary Regulations (2005). Harmonization with the International legislation on Biosafety and Biosecurity in medical settings is also in progress. National experts permanently take part in the International meetings on epidemiological surveillance, control and diagnosing of BPA, Biosafety and Biosecurity strengthening.

Taking part in the National Programmes and actively moves into the International society of Biosafety and Biosecurity, Ukraine needs improvement in:

- Legislation, harmonized with international (including EU) requirements.
- Laboratory Practices and Protocols.
- Biosecurity and Biosafety measures improvement.
- Trainings for personal in the International level.

Without doubt, effective overcome through international cooperation will allow for country improve national and effectively cooperate in the creation of the Global BIO Secure Environment.

TBD

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DISEASE SURVEILLANCE OF MULTI-DRUG RESISTANCE OF *M.TUBERCULOSIS* IN THE KYRGYZ REPUBLIC – USE OF BIOCHIPS WITH PULMONARY TB PATIENTS

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The Kyrgyz Republic is the country with high levels of incidence of tuberculosis. The morbidity rate of tuberculosis is 109 per 100 000 of the population and the mortality rate is 9.7 per 100 000. The problem is complicated with the high rate of multiple-drug resistant tuberculosis (MDR-Tb). The early diagnostics of the resistancy is the main problem. Diagnostics of MDR-Tb by the conventional bacteriological methods takes 2-3 months but the biochip oligonucleotide microarray assay could analyze the resistancy to rifampicin (RIF) and isoniazid (INH) in only 2-3 days.

In our survey the total 1542 samples obtained from patients with pulmonary tuberculosis were analyzed by Tb-biochip and conventional bacteriological method. The Rif, INH and MDR resistancies were studied. Mutations of rpoB, inhA, katG, and ahpC gene associated with resistancy were analyzed. In our study the sensitivity of the Tb-biochip was 93% and the specificity was 96.4%. The surveillance has revealed the high rate of drug resistancy even in the case of primary Tb (53% of cases) with the MDR Tb - diagnosed in 28.5% cases. The single drug resistance to RIF was 5.5% and to INH -19%. In the patients with histories of previous treatment the prevalence of drug resistance was 87% and MDR-Tb was in 75% cases. Single drug resistance to RIF was 4.0% and to INH - 8.0%. In penitentiary system 82% of patients were found to have drug resistance with the frequency MDR-Tb - 52%. Among all the rifampicin resistant strains the most common point mutations in rpoB gene were in codon 531 (60%), 526 (19 %) and 511 (6.8%). The point mutation Ser531→Leu was at the highest frequency (59%). Resistance to INH was associated with mutations in katG gene - 91%, inhA gene – 7% and ahpC gene -2%. In katG gene the most common mutation was Ser315→Thr (91%). In the inhA gene the only found mutation was inhA T_15 and in ahpC gene it was ahpC_9.

Conclusion: In Kyrgyz Republic it is a high prevalence of multidrug résistance Tb in primary Tb patients. The main reason of multi-drug resistancy are mutations Ser531→Leu of the rpoB gene and Ser315→Thr of katG gene.

IMPLEMENTATION OF NEW APPROACHES FOR DISEASES SURVEILLANCE IN GEORGIA WITH INTERNATIONAL COLLABORATION

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In 1996, under the frame of health reform, the Sanitary-Epidemiology Stations' (SES) network has divided into a two separate units: Sanitary Inspection and Public Health Service. However, Sanitary Inspection Service has been abolished in 2006. The National Center for Disease Control and Public Health (NCDC) has been delegated as a central agency for the public health.

As a part of decentralization process, Regional/District Centers of Public Health (CPH) were established by local governments. They implement surveillance, routine control measures and immunization programmes, coordinate other preventive activities on the regional/district levels.

Primary health care facilities are now free-standing independent legal entities. They provide state health programmes (which should be free or with co-payment requirement).

NCDC of Georgia was established on the basis of Georgian "Anti – Plague Station". The Statute, among other goals, functions and activities of NCDC, lists "carrying out surveillance", "detection of agents causing epidemics and outbreaks", "establishing national collection of bacteria and viruses", "development of legal documents, guidelines and recommendations for the Ministry of Health", etc.

Through the USAID funded project, new communicable diseases surveillance guidelines based on the WHO recommendations were implemented and functional, including updated standard case definitions, data recording and reporting system, case management, etc.

First sentinel surveillance system has been introduced for influenza, bacterial meningitis and rotaviruses by the financial and technical support of WHO and CDC, Atlanta.

Research grant projects (BTEP/ISTC, IPP/STCU, CBR/CTR, DST/UK) gave us the opportunity to strengthen laboratory-based surveillance.

Over the last few years several molecular methods for rapid identification and fingerprinting of different pathogens have been applied at the NCDC. These modern techniques strengthened laboratory's capabilities to rapidly respond to urgent public health threats and assist in the detection and tracking of these diseases. Application of genotyping techniques for investigation of NCDC Culture Collection enables to determine the extent of strain variability as well as define the ability of new molecular techniques to characterize potential biothreat agents circulating in the wild.

For detection of different bacterial and viral agents such as *B.anthracis, F.tularensis, Y.pestis, Brucella, Influenza A/H5* the conventional and Real-Time PCR techniques are used. Rapid and accurate laboratory diagnosis is a key to monitoring the presence of these organisms in natural foci and in cases of human disease and are essential to ensure proper control measures. Molecular methods, such as Pulse Field Gel Electrophoresis

(PFGE), IS (Insertion Sequence) element fingerprinting, have been applied for different infection agents such as *Y. pestis, F. tularensis, Salmonella, Ps.aeruginosa, St.aureus, Enterococcus, Cl.botulinum*. Recently acquired Sequencer gives opportunity to use different modern techniques (MLVA, SNP, Sequencing). Multiple-Locus Variable Number Tandem Repeat Analysis (MLVA) has been already applied in order to characterize bacterial isolates of *Y. pestis* and *F. tularensis* obtained from the different foci. Such characterizations help us to close a significant gap in our knowledge of strains present in this geographical region.

Molecular strain discrimination is proved to be a valuable approach to the epidemiological understanding of different pathogens.

DTRA/CTR programme provided support to strengthen integrated, secure and sustainable disease surveillance system in Georgia. EIDSS, developed through DTRA/CTR programme, strengthens and supports monitoring of dangerous diseases by integrating veterinary and human case and aggregated data, demographic information, geographical information including real time mapping of case events as these unfold, disease-specific clinical data (based on standardized case definitions), epidemiological information, sample tracking linked to each case and event, tests and test results linked to each sample into a cohesive information set that is continuously synchronized amongst all EIDSS sites within a country providing near real time information flow that can be then disseminated to the appropriate organizations in a timely manner.

SURVEILLANCE OF RICKETTSIALDISEASES IN UKRAINE (BTRP proposal P364)

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Arthropods are notorious vectors of various pathogenic protozoa, rickettsiae, bacteria, and viruses that cause serious and life-threatening illnesses in humans and animals worldwide. Screening of arthropods for such pathogens by using epidemiological tools may disclose the prevalence of arthropod-borne pathogens in particular geographic environments. Some of these agents, such as *Rickettsia prowazekii* (typhus fever), *Coxiella burnetii* (Q fever) are now recognized as important emerging vector-borne infections as well as agents that could be utilized as biologic weapons. Ehrlichial and rickettsial infections have been reported to exist in a broad band across Europe, Asia, Africa, and the Americas. Other arthropod-borne organisms, including some *Borrelia* and *Bartonella* spp., have also been shown to cause infections in animals and humans, and are transmited by different kinds of tick.

Pediculosis (lice infestation) is observed in all countries in the world and among all groups of people. Pediculosis is influenced by social, hygienic, and epidemiological circumstances. The louse-borne diseases, epidemic typhus (Rickettsia prowazekii) and trench fever (Bartonella quintana) are classically transmitted by body lice, while the role of head lice as vectors has not been fully resolved. Epidemiologic associations show that the louse can transmit Rickettsia prowazekii and Bartonella quintana simultaneously. Pediculosis as a public health problem has increased in the last few decades in many developed regions of the world. Head lice infestation, particularly of children, has become more important as pediatric health problem. At the beginning of the third millennium, the increase of pediculosis has not declined.

It is suspected that arthropod-borne infections are common in Ukraine. The Lviv Research Institute of Epidemiology and Hygiene (LRIEH) has a long history of investigating arthropod-borne infections throughout Ukraine, and has historical data on infections such as epidemic typhus.

Investigations of arthropod-borne diseases (louse-borne typhus, trench fever, Q-fever, other tick-borne rickettsial diseases, tick-borne and mosquito-borne arboviral infections, tularemia) what are include in Project UP-1/STCU P-364 will made for the first time in Ukraine. We will obtain the algorithm of the serological study of the seroprevalence of the arthropod-borne diseases. Further investigation into a wide variety of arthropod-borne infections, utilizing the expertise at the LRIEH, as well as CSES in Kiev and Anti-Plague Institute in Odessa, will provide useful information for Ukrainian public health and medical personnel. Full scale Investigating these infections can provide information that will improve disease recognition among physicians caring for patients in affected areas and provide guidance regarding the importance of control measures.

BIOLOGICAL PECULIARITIES OF CAUSATIVE AGENTS OF SOME BACTERIAL INFECTIONS IN KAZAKHSTAN (*Y.PESTIS & H.PYLORI*).

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Main features of 4000 *Y.pestis* strains isolated in natural foci of Kazakhstan during the last 10 years were studied. All the strains obtained from different rodents were typical. Range of features for the wild strains, such as presence and activity of FI-antigen, quantity of arginine dependent, Pgm^+ and Ca^- strains, virulence, biochemical activity correlated with ecological dependency and phases of epizootic process. The study allowed differentiation of local populations ("enzootic nuclei" and "epizootic zones") by the need of isolated *Y.pestis* strains in amino acids at 37°C. All isolated strains of *Y.pestis* were sensitive to streptomycin, gentamicin, tetracyclines, chloramphenicol and ciprofloxacin used to treat plague. Combinations of streptomycin and ciprofloxacin, streptomycin and doxycycline, streptomycin and chloramphenicol, gentamicin and ciprofloxacin should be considered as the optimal for the treatment of patients with plague. At the same time the single dose of streptomycin should be decreased form 0.5 gr. to 0.3 gr. and the frequency of uptake increased to allow the daily dose of 2,0 gr for adults.

Sixty seven *H. pylori* cultures obtained from mucoid lining of patients with erosive and catarhhal gastritis, duodenal and gastric ulcers were studied. Morphological, tinctorial and biochemical features of all the strains were typical. Sensitivity of the strains to the following drugs was studies: amoxicillin, clarithromycin, pefloxacin, gentamicin, ampicillin, oxacillin, cefazolin, azithromycin and metronidazole. All the strains (100%) were highly sensitive to clarithromycin and resistant to ampicillin, oxacillin and cefazolin. 55% of strains were highly sensitive and 45% sensitive to pefloxacin. 96% of strains were sensitive and 4% resistant to gentamicin. 83% of strains were highly sensitive and 17% resistant to amoxicillin, 72% of strains were highly sensitive, 4% sensitive and 24% resistant to metronidazole. Sensitivity to azithromycin was studies for 20 strains and all of them were highly sensitive to this drug. Analysis of the sensibility range shows relatively high level of resistance to amoxicillin (17%) and metronidazole (24%) which requires changes in the schemes of treatment used for patients with this pathology. Use of treatment schemes that include pefloxacin and azithromycin can be considered as promising during possible trials.

OVERWIEW ON TB IN THE WHO EUROPEAN REGION

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The total number of tuberculosis (TB) cases reported by the 53 countries of the World Health Organization European Region was slightly lower in 2006 than in 2005 (422,830 versus 426,457), reflecting a decrease in three-fourths of the reporting countries. Most TB cases in 2006 (73%) were reported by 12 former Soviet Union republics in the East, 21% by the European Union and West and 6% by the remaining countries in the Balkans. National TB notification rates ranged from 4 to 282 per 100,000 population. The total TB notification rate for the whole Region has increased very slightly between 2002 and 2006, from 46 to 48 cases per 100,000, although rates of previously untreated TB cases appear to be on the decrease in both the East and West.

The stabilisation in TB incidence in the European Region as a whole in the last few years marks a degree of progress in TB control. The TB caseload and incidence, however, vary considerably across the Region and weigh disproportionately on certain countries where information and resources are insufficient to implement the best-suited control measures. Rates are not decreasing everywhere, partly as a result of improved detection and fluxes in migration. These are major characteristics of the TB situation in the Region which will need increased attention in future. A high frequency of MDR TB as well as the presence of extensively drug-resistant TB (XDR TB), has now been well documented in patients presenting for treatment in most countries of the former Soviet Union. The HIV epidemic in countries of the former Soviet Union, predominantly among injecting drug users, is having a perceptible impact on TB. It seems that the increasing trend of TB cases reported among persons of foreign origin in several western countries has reached a turning point, as numbers declined between 2005 and 2006. Other sub-populations at increased risk of infection or unfavourable outcomes of treatment could benefit from targeted surveillance and outreach programmes.

BIOMARKERS IN TUBERCULOSIS

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Protection against tuberculosis is dependent on an efficient interaction between innate and adaptive immunity. The crosstalk between both arms of the immune system is mediated by chemokines and cytokines, ultimately resulting in T cell activation. In case of a successful immune response T cells release interferon-gamma and destroy infected target cells as well as intracellular mycobacteria. Measurement of these components-cytokines, lytic effector molecules and antimicrobial peptides- are therefore potential biomarkers that predict the outcome of infection with Mycobacterium tuberculosis. Biomarker identification is also essential for estimating the efficacy of potential vaccine candidates. While it takes decades to collect reliable results on vaccine efficacy against tuberculosis in the field, measurement of immunological responses is fast and could accelerate the identification of suitable vaccine candidates. Based on an overview of the human immune response to tuberculosis-good, bad and potential biomarkers will be discussed.

EPIDEMIOLOGICAL AND EPIZOOICAL FEATURES AND ORGANIZATION OF SANITARY AND EPIDEMIOLOGICAL SURVEILLANCE OF TUBERCULOSIS IN TAJIKISTAN

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ISTC SUPPORT FOR THE CREATION OF A RESEARCH CENTER FOR TB CLINICAL TRIALS

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RATIONALE AND BACKGROUND OF THE PROJECT. The key challenges in the treatment of tuberculosis include: 1) High prevalence of drug-resistant MBT strains, primarily multi- (MDR) and extended-drug resistance (XDR); it declines the efficacy of current standard treatment regimens at least twice or more. To date, treatment of MDR and XDR TB based on the less effective, more toxic and more expensive drugs, than those used as first-line drugs. 2) Non-compliance of patients with the treatment, caused by theirs specific social and behavioral features and the poor treatment tolerability due to the treatment adverse events (since the so-called "short-term therapy" must be administered for a minimum of six months). Although new anti-TB would alone not solve these problems, their logical use would greatly improve the results of treatment for many patients.

OBJECTIVES OF THE PROJECT is to develop the capacity to conduct randomized, controlled clinical trials (RCT) of new drugs and drug regimens for the treatment of TB, including MDR- and XDR-TB, taking into account the Russia uniquely suited for TB clinical trials because trained personnel and large numbers of TB patients co-exist.

The Collaborating Institutions are

- Research Institute of Phthisiopulmonology, Sechenov Moscow Medical Academy(RIPP - clinical enrollment and certain bacteriological investigations)
- State Research Center for Applied Microbiology, Obolensk (SRCAM - genetic analysis of mycobacterial isolates)
- US Centers for Disease Control and Prevention, Atlanta (CDC - technical assistance)
- Foundation for Innovative New Diagnostics (FIND - technical assistance)

AIMS OF THE PROJECT

- Build laboratory, clinical, and computer infrastructure required for RCTs at RIPP
- Enhance laboratory capacity at SRCAM for molecular genetics in support of RCTs
- Provide data management, statistical, and laboratory training for the conduct of RCTs
- Design and conduct a Phase II RCT of a TB treatment regimen that includes moxifloxacin in the initial two-month phase TB treatment
- Compare TB drug susceptibility testing methods

RESULTS. The total number of personnel, involved in the Project, is about 30 in RIPP and 10 in SRCAM. The project consists of two phases. Phase I: upgrading facilities at RIPP (10-room hospital ward including a ventilation assessment), upgrading laboratory and computer facilities at RIPP and SRCAM (ultrasonic nebulisers for sputum induction, spectrophotometer, BACTEC MGIT 960, Automated sequencer, state-of-the-art computers and software), hiring and training project personnel (project coordinator, data manager, microbiologists, lab

technicians, computer programmers, data entry persons, physicians, nurse coordinator, nurses), developing protocol and obtaining IRB approval – all items are achieved and now the Phase II - the randomized clinical trial – is performed. It's the first RCT in Russia,

Randomized Clinical Trial "Evaluation of the safety and microbiological activity of a moxifloxacin-containing regimen compared to a standard control regimen in the first two months of treatment (i.e. the initial phase) of newly diagnosed sputum smear-positive patients" on November, 15, includes 57 patients (34 – with completed intensive phase of treatment) – 25% of the planned sample size.

THE PLANNED PROJECT OUTCOMES

- Information to undertake Phase III efficacy studies that will be needed for registration/approval of moxifloxacin as a drug for treating tuberculosis
- Information required for modification of standard TB treatment regimens in Russia
- By developing sustainable infrastructure for conducting clinical trials at RIPP, it is anticipated that RIPP would become the coordinating center for the conduct of multicenter TB trials in the Russian Federation

ANTIBIOTIC RESISTANCE: ANTIBIOTICS AND BACTERIA

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Since the forties there have been many antibiotics introduced on the market. Most of them (beta-lactams, aminoglycosides, macrolides, tetracyclines, pomymixines…) derived from natural molecules. They have been chemically modified either to enhance their pharmacological properties, to increase their efficacy toward different bacteria, to extend their spectrum of activity or to resist to existing or new mechanisms of resistances. Only few molecules are completely synthetics such as the oxazolidones and the quinolones. These antibiotics aims to combat the most prevalent bacteria responsible for the community or hospital acquired infections due to aerobic and anaerobic bacteria in*cluding Pneumococcus, Enterobacteriaceae, Pseudomonaceae as well as* ***Staphylococci*** *and Enterococci*. Once an antibiotics was used for the treatment of infectious diseases resistance occurred either because the organism was able to activate a mechanism of resistance that it already harboured (Chromosomal □-lactamase for example) or after one or multiples steps due to modification of one or several targets of these molecule. One of the most successful examples is that of *Mycobacterium tuberculosis* which could easily acquire spontaneous resistance to all antituberculous drugs if they were not given in association. For some molecules such as glycopeptides it tooks years before the appearance of spontaneous resistance giving the opportunity for the bacteria to find other easier transferable pathways to develop resistance. The other main mechanisms of resistance is the acquisition of resistant genes from clothe or distant species in the environment either by direct introduction of pieces of chromosomes or after transfer of genetic elements which themselves can accumulate all variety of resistant cassettes. Interestingly the introduction of certain antibiotics successively in the hospital and then in the community as consecutively raised the emergence of similar but not identical resistances in these two worlds (extended spectrum beta-lactamases). One of the essential factor for a resistant pathogen is its capability to disseminate in the population as it was the case for penicillin resistant *Pneumococci,* in the community, or methicillin resistant *S. aureus* in the hospital and more recently in the community as well. Such dissemination is also becoming planetary through easy transportations. Very early, bi-therapies put forward as a solution to avoid resistance and to increased effectiveness (synergy) on the target strains. However the concept shows many limitations including the requirement to get, at the same time, enough of the two molecules at the site of infection. Some species such as *P. aeruginosa* and *Acinetobacter* are at higher risks taking in account their propensity to accumulate resistances through chromosomal mutations (target , efflux) or acquisition of transferable material. Other bacteria such as *E. coli* known to be accessible to many antibiotics very slowly and scarcely evolve toward toto-resistance. Finally while usage of different antibiotics against different species does not lead immediately, to high level resistance they allow accumulation of low level resistance. Even if this low level resistance is still under the critical concentrations of antibiotics sufficient for the eradication of the bacteria it introduces in the environment species which will during subsequent therapy develop high level

resistances. In conclusion, the fact that resistance appears toward a molecule is unfortunately a mark that this molecule is active. For this reason it unlikely that soon or later a resistance will not appear toward a specific antibiotic. It explains why new molecules will always be needed and most importantly why we have the obligation to make the better usage of the existing antibiotics to allow their longest possible survival.

OVERVIEW OF EMERGING ANTIMICROBIAL RESISTANCE IN RUSSIA

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The development of antibiotic-resistant bacteria in any country is of global importance. Antimicrobial consumption is recognized as the main cause of emerging resistance. Though the data on antimicrobial consumption in Russia are limited one important issue is well established. Hospital use of antimicrobials in Russia is practically the same as in EU countries (for example in France) 2.13 and 2.32 DDD per 1000 inhabitants and per day respectively. But outpatient use of antimicrobials differs significantly – 27.9 DDD in France and 9.6 DDD in Russia. The differences in selective pressure may explain relatively low resistance rates among major community-acquired pathogens, and high levels among hospital-acquired pathogens.

According to cumulative data from a number of national surveys (from 1998 to 2007) the prevalence of antimicrobial resistance among *Streptococcus pneumoniae* varies in different geographical regions being highest in large cities (Moscow and St.-Petersburg) and significantly lower in other regions. In 2002 in Moscow 23.8% of isolates were nonsusceptible to penicillin, and in 2007 – 15.8%. The highest rate of resistance to macrolides was observed in Moscow in 2003 – 19.0%, in 2007 resistance demonstrated 11.2% of isolates. Mechanisms of resistance to macrolides included *erm*(B) alone (50%), *mef* alone [*mef*(E), *mef*(I), or a different *mef* subclass; 19.7%], or both *erm*(B) and *mef*(E) (30.3%). Isolates with dual resistance genes [*erm*(B) and *mef*(E)] belonged to clonal complex CC81 or CC271. The prevalence of resistance to ampicillin in *Haemophilus influenzae* due to production of β-lactamases never exceeded 5%, β-lactamase negative ampicillin resistant isolates are rear.

Among community-acquired pathogens high rates of antimicrobial resistance in *Neisseria gonorrhoeae* are of major concern. During 2005 and 2006 4.7%, 48.3%, 69.5%, and 76.6% of isolates displayed intermediate susceptibility or resistance to spectinomycin, ciprofloxacin, tetracycline and penicillin, respectively.

Extremely high rates of resistance in Gram-negative bacteria from ICU to 3rd generation cephalosporins due to production of class A and class C β–lactamases significantly compromises patient management in Russia. In some centers up to 100% of *Escherichia coli, Klebsiella* spp., and *Proteus* spp. isolates are resistant. ESBL's and particular CTX-M-1 group β-lactamases are predominant in Enterobacteriaceae. In one study plasmid-mediated AmpC β-lactamases (MOX-2, CMY-1, CMY-2, DHA-1, LAT-1 and MIR-1) were detected in 16% of *Klebsiella* spp. isolates resistant to extended spectrum cephalosporins. Resistance of Gram-negative bacteria to carbapenems due to production of acquired metallo-b-lactamases (MBLs) is an increasing international public health problem. The problem of MBL producing strains in Russia was originally confined to *Pseudomonas aeruginosa*. Production of MBLs, mostly VIM-2, was identified in *P. aeruginosa* isolates from various geographic regions of Russia. In 2006

the emergence of the *E. coli* strain that co-produces VIM-4 and CTX-M-15 b-lactamases was reported.

The prevalence of MRSA in different ICU's in Russia varies from 0 to 80%. According to the recent publication more than 90% of MRSA isolates from ICU's in Moscow belonged to CC8/239 and small number of isolates - to CC1 and CC5. Outbreaks of nosocomial infections due to vancomycin-resistant *Enterococcus faecium* harboring *van*(A) gene clusters were observed in hematological units.

Improvement of hospital hygiene, microbiological diagnostics, education of medical staff and patients are needed to contain antimicrobial resistance in Russia.

BACTERIOPHAGES FOR acteriophages for Treatment of Diseases Caused by Antibiotic Resistant Pathogens

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G. Eliava Institute of Bacteriophages, Microbiology and Virology, Tbilisi, Georgia (founded in 1923) is one of the famous Institutions focused on bacteriophage research, elaboration of appropriate methodologies for biological preparations for human and animal protection. The main direction of the Institute is construction of phage preparations against infectious diseases, including those caused by antibiotic-resistant bacterial strains. The institute has a substantial collection of bacteriophages active against different human, animal and plant pathogens.

Currently, the Institute has a scientific part and a small, experimental production. We produce several products for a limited number of patients. We are producing phage preparations against intestinal disorders (**Intesti phage**) and purulent-septic infections (**Pyophage, Enco-phage, SES**). These preparations are mixtures of phage lysate filtrates active against different bacterial pathogens. One of the successful preparations elaborated at the Eliava Institute and Georgian Technical University is "**PhagoBioDerm**", which includes original biodegradable polymers impregnated with bacteriophages against *Staphylococcus, Streptococcus, Pseudomonas, E.coli, Proteus, Klebsiella, Acinetobacter.* An original technology is developed at the Institute for preparing bioactive composite acting in bacteriophages' sustained/controlled release fashion. This preparation shows high effectiveness in treatment of superficial injuries like burns, bedsores, tropic ulcers (including ones of diabetic origin), infected wounds and stings, etc. The "PhagoBioDerm" wound dressing is especially convenient in field conditions when no or rare qualified medical aid is available.

Phage preparations are successfully used as therapeutical agents against various infectious diseases caused by multi-drag resistant pathogens. The best example of phages against antibiotic-resistant bacterial strains is Staphylococcal bacteriophage that is examined on the MRSA strains from the UK and DZMZ (Germany) collection *in vitro*. It showed high activity (99.5%) against these strains.

The Institute plans to continue and extend its activity for elaboration of phage preparations and to explore the most appropriate organizational development for broader production, application and marketing of its biological preparations.

Induction of organism's protective resources to chemical and bacterial toxins

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Nowadays physicians are faced with the serious problem of ineffectiveness of a wide range of antibiotics and other pharmacological antibacterial remedies in treatment of bacterial infections. Such ineffectiveness of conventionally applied drugs is related to a high mutation rate of the bacterial species and, hence, to formation of bacterial species which are insensitive even to relatively novel antibacterial drugs. This leads to poor recovery and serious complications of infectious diseases in patients and even to their death.

A novel serotonin-modulating anti-consolidation protein (SMAP) was identified and purified from rat brains (Mekhtiev, 2000). SMAP consists of two subunits with molecular mass of 60 and 126 kDa, is tissue non-specific and being in linear relationship with serotonin level. Our earlier studies showed that significant decrease of this protein content in the gobies liver dwelled in the polluted zone of the Caspian Sea parallels to increasing of mutagenicity level, while short-term exposure of fish in the oil-contaminated water leads to upregulation of SMAP without mutation formation (Mekhtiev et al., 2005). These data gave grounds to a conclusion of antimutagenic and antitoxic activity of serotonergic system. The studies to analyze this idea were conducted on one-year sturgeon juveniles. Animals were culled into three groups: 1) control group – animals were kept in fresh water; 2) 1st experimental group – animals were kept in the water contaminated with sediments from the Baku Harbor containing high levels of heavy metals and PAHs, for 7 days and later were put into the pure water; 3) 2nd experimental group – animals were twice administered intramuscularly with SMAP protein (1.5 mg): prior to their exposure to sediment-contaminated water (7 days), and before putting them into the pure water. After exposure blood samples were taken and subjected to micronucleus analysis to evaluate the mutagenicity level. The results showed that in the 1st experimental group acute increase of mutation level ($p<0.001$) was observed. On the other hand, the intramuscular injection of SMAP into the animals leads to a significant decrease ($p<0.01$) of mutagenesis relatively to the animals from the 1st experimental group. So, artificially increasing the serotonergic system activity by administration of SMAP protein prevented and inhibited formation of mutations induced by industrial-polluted sediments. Our recently conducted studies showed that antimutagenic and antitoxic activity of SMAP protein is mediated through upregulation of heat shock proteins (HSP) (Mekhtiev et al., 2008). Issuing from the non-specific character of HSPs' protective activity in the organism (Sharp et al., 1999), a conclusion of universal antitoxic activity of serotonergic system towards the toxins of different origin (chemical and bacterial) is put forward.

BENEFITS OF JOINING THE ISTC's PARTNER PROGRAM

Albert Gozal, International Science and Technology Center, Moscow, Russian Federation

ISTC - Partner Program

Partnering with ISTC allows organizations interested in expanding their R&D and Innovation pipelines access to more than 900 ISTC affiliated laboratories in Russia and CIS, more than 200 of which do Biotech research and product/service development, contract research, preclinical trials, sample analysis...

Advantages of becoming an ISTC Partner include:

- Cost free matchmaking services, e.g., call for proposals and expertise/facility identification, in-country logistical support, and other services to help Partners find technology providers in Russia/CIS that meet their innovation needs.
- Competitive project labor and overhead costs in Russia and CIS.
- Tax and custom exemptions, including tax free participant salaries that further lower project costs.
- Direct and transparent payment to CIS scientists.
- Assistance with and knowledge of Russian/CIS Export Control.
- IPR that is integral to Project Agreement, i.e., negotiated before the project starts.
- Total "turn-key" project management using ISTC proven procedures and personnel.
- Complete control of project funds by Partner and full reporting of project financing.
- More than 14 years of proven total project management at R&D Russian and CIS laboratories.
- Quarterly technical and financial reporting on each project.
- Low project management fee (5%) for commercial Partner projects.
- ISTC staff with extensive knowledge of Russian and CIS technological and business environments.

Results from Regular Projects

Of the more than 600 ongoing or completed Biotech related projects at ISTC, more than 250 were funded by Party Countries (Regular Projects), thus there is no funding Partner (commercial entity) that has direct rights to results and Intellectual Property generated from the project. This gives the possibility to negotiate IPRs, product licenses, follow-on R&D or other mutually beneficial arrangements (i.e., benefit from past investments). A few examples of completed Regular Biotech projects include:

#1758 Superantibodies, Next-Generation Therapeutic Agents for Diagnostics and Treatment of Infections

#1781 Design and Studies of New Anti-Virus and Anti-Tumour Agents Based on Stable Addressed Liposomes Carrying Lipophilic Drug Derivatives..

#1848 Screening, Identification and Study of New Antibiotics, Active Against Multi-Drug Resistant Microbial Agents.

Opportunities

More than 550 project proposals related to Biotechnologies have been approved by ISTC review boards but could not be implemented due to lack of funding, e.g.,

- #3729 Antimicrobial Activity of Bacteriophages and Their Lytic Products to Pseudomonas aeruginosa Clinical Isolates.
- #2960 Development of a Remote Method for Bacteria Detection with Using Mass Spectrometry.
- #2998 Development of Live Culture Influenza Vaccine.
- #1898 Investigation of Cellular and Human Immunities Induced by Chemical and Live Anthrax Vaccines.
- #3604 Immuno-Technology for Express Detection of Mycotoxins at Nano-Scale Concentration in Food Products.
- #K-1273 Biologically Active Nutrient Supplements that Produce Protector and Detoxication Effect on Organisms
- #3595 Composite Coatings Based on Natural and Synthetic Polymers Containing Porphyrins and Amphiphilics for Photodynamic Treatment of Skin Burns and other Wounds.
- #3496 Antidepressants and Monoamine Oxidase Inhibitors as Anti-Alzheimer's Disease Agents.

A number of our beneficiary Biotech institutes, laboratories and spin-off companies are interested in developing business relations with foreign companies for their products and services that are on the Russian/CIS markets or are near-market

Partnering with ISTC will allow companies and organizations access to ISTC services and network of affiliated Russian and CIS laboratories, institutes and companies with no "up-front" obligations or costs.

OVERVIEW OF MULTI-DRIG RESISTANCE TUBERCULOSIS

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GENETIC DIVERSITY AND POPULATION STRUCTURE OF *M.TUBERCULOSIS* STRAINS CIRCULATING IN CENTRAL RUSSIA

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We studied genetic diversity and drug susceptibility pattern of *M. tuberculosis* strains recovered from culture-positive pulmonary TB patients in Central Russia.

Methods. Genetic diversity was analyzed using a sample of epidemiologically unlinked strains of *M. tuberculosis* recovered in the Moscow, Tula, and Kaluga regions in 1998-2006. For population-based study all culture-positive TB patients diagnosed in Tula TB prophylactic centre and all patients of Ozerki prison hospital (Tula region) during 2001-2002 were enrolled. Drug susceptibility testing for isoniazid, rifampicin, ethambutol, streptomycin, and kanamycin was performed using method of absolute concentrations. Epidemiological markers, such as a number of tandem repeats in DR locus, IS*6110*-RFLP pattern, and MIRU-VNTR typing along with phylogenetic characteristics were analyzed. Prevalence of mutations conferring drug resistance was examined.

Results. Analysis of *M. tuberculosis* phylogenetic groups prevalent in the region revealed moderate diversity: members of four from seven SNP clustered group were found. One hundred and five different IS*6110*-RFLP patterns, 72 different spoligotypes, and 56 unique MIRU-VNTR patters were identified within the sample. Genetic distance was calculated using Jaccard's distance matrix and corresponding phylogenetic trees were built. Members of ancient SCG2/PGG1 and modern SCG5/PGG2 showed relatively short genetic distances within their group. Members of SCG3/PGG2 and SCG6/PGG3 groups were less common and showed more divergent genotypes.

Study IS*6110*-associated polymorphisms in *plcABC* locus of *M. tuberculosis* revealed that majority of SCG5/PGG2 were clonal variants of the strain we designated as LAM-RUS. This strain is characterized by IS*6110* insertion into a unique position in *plcA* gene.

Comparative analysis of population structure of *M. tuberculosis* strains recovered in Tula TB prophylactic centre and Ozerki prison hospital during 2001-2002 showed high rate of clustered cases in both settings. Largest clusters were identified in LAM-RUS and Beijing families. Although major *M. tuberculosis* strains circulating in the sentinel and civilian population was essentially the same, higher overall level of clustering and rate of MDR TB among the new patients were found in the prison hospital. Clusters comprised from isolates recovered in both prison and civilian hospitals, emphasizing the interdependence of two populations.

High rate of drug resistant strains was observed in the region: less than 20% cases in the civilian population and about 9% cases in penitentiary were sensitive to all drugs tested. Thirty five % cases in Tula TB centre patients and 71% cases in prison hospital were MDR TB.

100% of MDR cases in the prison hospital and in civilian setting were due to a limited number of *M. tuberculosis* strains, belonging to LAM-RUS and Beijing family. Abundance of MDR strains and MDR strains resistant to kanamycin circulating in the region are of major concern implying the threat of XDR TB epidemics.

Conclusion. *M. tuberculosis* Strains LAM-RUS and Beijing families are major contributors to the TB epidemiological picture of the studied population.

DIAGNOSIS OF MDR-TB

Elvira Richter, NRC for Mycobacteria, Borstel, Germany

The increasing incidence of resistant and multi-drug resistant *M. tuberculosis* strains is a global problem. The rapid determination of drug resistance is a prerequisite for the onset of an effective antimicrobial therapy and thus preventing further spread of drug resistant isolates. Due to this, laboratories are challenged to provide rapid drug susceptibility results for first-line, but also for second-line drugs. Conventional drug susceptibility testing (DST) is performed on solid media, but requires at least 3 to 4 weeks of incubation. The introduction of liquid media for DST has markedly shortened the time required to obtain susceptibility results. Today DST can be performed within 7 to 10 days using automated liquid culture systems. Furthermore, testing of new drugs can also more easily be run in these systems. The most rapid methods for detection of resistant strains are based on the confirmation of genetic mutations which are known to confer resistance to specific drugs. Commercially available line probe assays enable the rapid assessment of multi-drug resistance by detection of mutations causing resistance to RMP alone or to both RMP and INH. These techniques are not only applicable for culture isolates of *M. tuberculosis* but also for smear positive sputum samples, thus accelerating diagnosis of MDR-TB to few days.

NEW BIOPHOTONIC METHOD AND NANOSTRUCTURE SENSOR INSTRUMENT FOR DIAGNOSTICS OF TUBERCULOSIS ACTIVA FORM

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Based on statistical data of World Health Organization an infectious disease of tuberculosis (TB) takes today leading place on a mortality among all infectious diseases. The cause of it are following factors: *Mycobacterium tuberculosis* pathogenic organism possesses sufficiently large incubation period; duration of a clinical course; latent character symptoms implications at initial stages; impossibility to diagnose of TB some forms by modern methods; low selectivity of existing methods of diagnostics; TB drug resistance etc.

In the world for tuberculosis ***testing billion of dollars*** *are* spent, and for treatment ***medicaments*** of this illness about ***300 million dollars*** *are* spent.

Doctor Mario Ravilone (the director of WHO department for tuberculosis prevention) in the report has noted: “New, safe and inexpensive diagnostic systems are urgently necessary for simplification of revealing of tuberculosis cases for the world”.

TB Diagnostics is accompanied by a number of problems:

- complexity and use of lager number both reactants and laboratory materials (direct microscopy with Ziehl's-Nilsen staining, inoculation of dense nutrient medium by Liovenstein-Ensen or Finn, use of liquid nutrient mediums);
- duration of analysis carrying out (from 6 hours to 3 months), except for a computer tomography and roentgenofluorography;
- allergic reactions of the patient and drug intolerance (Mantoux and Koch skin tests);
- the low percent of revealing or discrepancy of analysis results (microscopy with a staining, luminescent microscopy, skin tests);
- unknown strain of *Mycobacterium tuberculosis*;
- later revealing of destructive damages (a computer tomography, photoroentgenography).

Having in mind above mentioned, in the present work essentially new method and the sensor instrument for tuberculosis diagnostics that is based on symbiosis of two different directions – nanophotonic and medicine - are proposed.

Well-known, that the pathogenic agent, getting to a human body, shows toxic action: some microorganisms, such as botulism, allocate toxins, but *Mycobacterium tuberculosis* differs by its latent nature. Infection process by *Mycobacterium tuberculosis* is not characterized by excretion of specific substance with the unique molecular formula, characteristic only to this disease.

Having carried out preliminary researches of group of patients infected with active pulmonary tuberculosis by co-authors of Science and Technology Center in Ukraine (STCU) Project #4495, it has been allocated the list of typical substances – so called TB markers. These

substances have organic character and are revealed as a result of protease and antiprotease systems functioning disturbance. As a result of activation of a proteolysis and definite biochemical processes there is an accumulation of some quantity of the specific TB markers, separated by us. So the essence of our work is detection of such markers by electrochemiluminescent technology realized in the sensor instrument based on use of modern nanomaterials, as detector elements for TB markers. The proposed method and the sensor instrument are possessing a number of advantages: early TB diagnostics, a low limit of detection, short time of the analysis (several minutes), possibility of repeated use of the developed sensory device, simple updating for detection of other biologically significant substances, cheapness of the device and an analysis method.

GEL-BASED BIOCHIPS FOR CLINICAL APPLICATIONS: DETECTION OF PATHOGENIC BACTERIA AND VIRUSES, DRUG-RESISTANT SPECIES IDENTIFICATION, ANALYSIS OF HUMAN GENOME POLYMORPHISMS

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An original nanotechnology of biological microchips (biochips, microarrays) has been developed at the Engelhardt Institute of Molecular Biology, Russ. Acad. Sci. (EIMB), which allows to perform multi-parametric analysis of biological samples. The gel pads of a biochip bear highly specific probes (fragments of DNA or proteins) which interact selectively with the complementary sequences of tested DNA or protein thereby allowing to quantitatively determine their presence in the analyzed material. The following certified biochip-based test-systems are manufactured by EIMB' spin off company "Biochip-IMB", Ltd, and used in Russian clinics:

- "TB-Biochip" and "TB-Biochip-2" for detection and analysis of TB strains resistant to first line drugs (rifampin & isoniazid) and to second line drugs correspondingly;
- "LK-Biochip" for identification of chromosomal translocations correlating with defined types of leucosis;
- "PF-Biochip" for analysis of predisposition to some types of cancer and for testing individual tolerance of certain therapeutic treatments.

Also, the biochips are developed which allow one to identify and analyze:

- Influenza type A viruses (30 subtypes) including the avian flu H5N1
- HIV-1, Hepatitis B and C, Herpes simplex and VZ viruses
- Extremely dangerous infections (smallpox, anthrax, plague, etc.)
- Genetic markers of an individual (in forensic studies)
- Causative agents of smallpox, anthrax and plague, the orthopoxviruses discerning them from other pathogens, similar in clinical presentation;
- Staphylococcus toxins, the toxins of cholera, diphtheria, tetanus and anthrax toxins, as well as ricine and vascumine.

Additional details concerning development and practical use of Russian biochips in the clinic are presented in our recent review articles:

- Mikhailovich V.M., Gryadunov D.A., Kolchinsky A.A., Makarov A.A. and Zasedatelev A.S. "DNA microarrays in the clinic: infectious diseases" (2008) BioEssays, v. 30, 673–682.
- Rubina A.Yu., Kolchinsky A.A., Makarov A.A., Zasedatelev A.S. "Why 3-D? Gel-based microarrays in proteomics" (2008) Proteomics, v. 8, 817-831.

OVERVIEW TB-VAC, EU PROJECT: NEW CANDIDATES FOR TB VACCINES

Brigitte Gicquel, Pasteur Institute, Paris, France

REFINED MOUSE MODELS OF VACCINATION AGAINST TB INFECTION

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Due to a highly variable performance of BCG vaccine in different populations and its doubtful efficacy against pulmonary TB in adults an ugrent need for novel TB vaccines is generally accepted. We are exploring two experimental approaches in order to improve vaccination strategy.

First, highly attenuated *M. tuberculosis* strains bearing multiple knock-out mutations of Rpf genes proved to be at least as efficient as BCG in defending B6 mice against subsequent TB challenge. We demonstrated that their residual virulence is not higher than that of BCG, as is the level of persistence in the lungs and lymphoid organs. We expect potential superiority of these novel live vaccines over BCG within the frames of the prime-boost strategy: boosting of the host with important antigens encoded by the genes from the RD1 region is possible if priming has been done with *M tuberculosis* mutants, but not with BCG lacking these genes. This hypothesis will be studied in the near future.

Second, within the frames of the ISTC-funded project #3257 we are studying several aspects of BCG vaccination via the oral route – technical and safety advantages of this technique over intradermal or subcutaneous injections are obvious. Our results show that oral BCG vaccination is quite efficient when applied to the newborn mice, but not adults. Whilst the degree of BCG dissemination, its loads in organs and peculiarities of immune responses elicited in newborn and adult animals are presently under study, it should be emphasized that BCG vaccine is normally given to the newborn humans. Taken together with our results in protective experiments, this suggests that the ban on human BCG vaccination via the oral route has not been adequately validated.

ATP SYNTHASE? AN EXCITING NEW TARGET FOR TB

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We discovered a diarylquinoline (TMC207 or R207910) with potent bactericidal activity against drug-sensitive and drug-resistant Mycobacterium tuberculosis. Whole genome sequencing of resistant mutants suggested that the drug targets the energy supply of mycobacteria by inhibition of the ATP synthase. The oligomeric subunit c (AtpE) of ATP synthase was validated as the target by genetic, biochemical and binding assays. Unlike other TB drugs, TMC207 is equally active against growing and dormant TB bacilli, making it a good candidate for shortening TB therapy.

In mice, four weeks of TMC207 monotherapy exceeds the bactericidal activities of isoniazid and rifampin by at least 1 log unit. Substitution of rifampin, isoniazid, or pyrazinamide (the World Health Organization's first-line treatment regimen) with TMC207 accelerated bactericidal activity, leading to complete culture conversion after 2 months of treatment in some combinations, against 5 months for the standard regimen. Four months of treatment with rifampin + pyrazinamide + TMC207 yielded the same relapse rate as six months of the standard regimen. Similar improvements were observed when TMC207 was combined with drugs to treat MDR-TB, suggesting that use of TMC207 may also significantly reduce the treatment duration for MDR-TB.

The bactericidal activity of TMC207 was confirmed in patients in a one week early bactericidal activity trial and the drug is now being investigated in a phase 2 trial in MDR TB patients

Synthesis of compounds with antituberculous activity

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Tuberculosis epidemy in Ukraine is the officially confirmed fact. Because of it, a development of new effective drugs against this disease at the conditions of nowadays Ukraine is an urgent necessity. A problem of tuberculosis treatment is very difficult because of many factors. The most significant among them is genetically conditioned variability of Mycobacterium tuberculosis proteins, which are cellular targets for antitubercular drugs. Therefore, most expedient and perspective is strategy of search and use in clinical practice of new drugs, the targets of which are exactly the most conservative proteins of Mycobacterium.

Among potential and actual mycobacterial targets, the FtsZ-proteins providing bacterial cell division satisfy this requirement best of all. The sequences of their globular parts are conservative enough, and their spatial structures have a high level of similarity not only within FtsZ-protein family, but they also are very close to the three-dimensional structures of eukaryotic α- and β-tubulins.

Basing on our own experience of structural docking of different antimicrotubular drugs and preliminary information about effective inhibitors of bacterial FtsZ polymerisation, we can consider benzimidazole and phenylcarbamate derivates as the most likely candidates to prevent a polymerisation of FtsZ-proteins. This supposition is based on two arguments. At first, these compounds are able to specifically bind by β-tubulins from any organic kingdom and share the same interactive site on tubulin surface at that. Secondly, an ability of benzimidazole/phenylcarbamate to inhibit a prokaryotic cell division was shown earlier for some bacteria species.

Information about the structural features of interaction of mycobacterial FtsZ protein with benzimidazoles/phenylcarbamates, in particular, about localization of proper binding sites on FtsZ surface, can enable a design of new active benzimidazole/phenylcarbamate compounds to be used as effective drugs for tuberculosis treatment. Technical approaches to identify specific biding sites on tubulin surfaces developed by us and based on the analysis of features of spatial structure of interacting components, can be successfully applied for solution of this problem. Necessary pre-condition for it is exact information about three-dimensional structure of Mycobacterium FtsZ, that in turn stipulates a necessity of development of their more detailed three-dimensional model, as an existent spatial model got from crystallography analysis of is incomplete and contains substantial gaps in globular part of protein. That will allow to carry out a correct in silico docking of these compounds with FtsZ and following development of technologies of rapid screening of known chemical compounds on their biological activity in relation define cell targets, rational design of

antitubercular drugs of new generation and application of new effective antituberculous compounds with FtsZs depolimerization activity in clinical practice.

NOVEL INDOL-CONTAINING CONDENSED TETRACYCLIC SYSTEMS WITH PROMISING HIGH ANTITUBERCULAR AND ANTIVIRAL ACTIVITY: SYNTHESIS AND SCREENING

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The basic statistics of the present-day global "tuberculosis problem" are well known: one-third of the global population is considered infected; 6 million new cases each year; 20% of adult death and 6% of infant deaths are attributable to TB. The increased incidence of drug-resistant tuberculosis certainly highlights the need for new antitubercular drugs. Equally urgent is the need for new antiviral agents, especially with the growing concern for the next influenza pandemic.

Our strategy is based on literature precedents that show that the combination of two pharmacologically active bicyclic systems in one molecule can promote the increase of biological activity of the molecule and expand the spectrum of its pharmacological action.

Indole chemistry turned out in the focus of chemists and pharmacologists after it was established that this fairly simple compound and its derivatives had strikingly versatile physiological activities.

Brief list of **indole** derivatives having unique physiological activities and performing vital functions in living organisms: **Serotonine** – performing mediator and modulator (neuro-hormonal) function in central nervous system (CNS), **Tryptophane** - naturally occurring essential amino acid, **Heteroauxin** - one of the main plant growth regulators, **Mexamin** and **Indralin** – efficacious radioprotectors, **Melatonin** – hormone of epiphysis, **Indophan** – stimulator and anti-depressant, **Indometacin** - one of the most powerful non-steroidal anti-inflammatory preparations, **LCD-25, Psylocin, Psylocibin** - well-known synthetic preparations of psycho-mimetic actions,

Metisazon® (Marboran®) –effective preparation against variety of smallpox.

The determination of tetracyclic nature of alkaloids of Pumpkin curare – **C-Curarin-1**, **Reserpine,** and especially high active anti-tumor drugs – **Vinblastine®** and **Vincristine®** (isolated from plants *Cataranthus roseus*) promoted the search for synthetic methods of tetracyclic condensed systems.

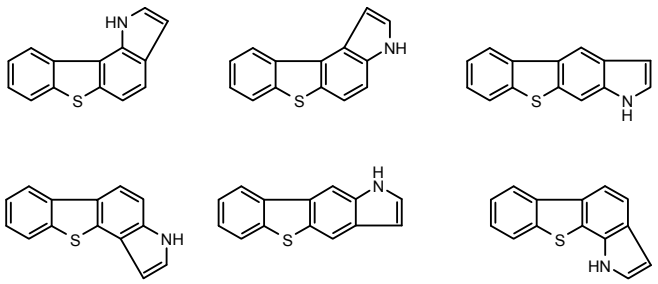
In our study, the basic bicyclic system is indole. Since the nature of the second bicyclic system is crucial for the pharmacological activity of tetracyclic construction, we have chosen benzo[b]thiophene and benzo[b]furan as the bicyclic partner for.

Our team (Scientific leader Prof. T.Khoshtaria) has more than 30 years expertise and experience in the synthesis and study of condensed tetracyclic systems. Wide family of new indole-containing condensed tetracyclic systems – pyrrolocarbazols, benzo[b]furoindoles, benzo[b]thiopheneindoles, pyrroloacridines, pyrrolophenothiazines and their dioxides, pyrrolcumarines, pyrrolophenoxantines and their dioxides were synthesized.

Pharmacological studies of tetracyclic condensed systems obtained were started in the All-Union Scientific-Research Chemical-Pharmaceutical Institute, Moscow, showed that tetracyclic indole-containing condensed systems have a wide range of physiological activity. According to experimental data obtained, several derivatives of some isomeric

benzo[b]thiophene indoles showed tuberculostatic activity much higher and toxicity much lower than **Isoniazid®** - the well known and widely used anti-tubercular preparation. Unfortunately these pharmacological investigations were ceased after disintegration of the former USSR.

Several years ago we have begun collaborating with the US NIH's NIAID-sponsored compound screening programs, the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF), (See www.taacf.org) and more recently, the Antimicrobial Acquisition and Coordinating Facility (AACF) (See www.niaid-aacf.org), which provides us with compound screening services against tuberculosis and 30 viruses (including influenza A and B strains), respectively. More than 150 compounds, derivatives of all isomeric benzo[b]thiophene- **(S=S),** and benzo[b]furan-indoles **(S=O), (**See below figure**)** have been sent for screening. Many of them showed high anti-tubercular and antiviral *in vitro* activities as we predicted. The data obtained are presented.



BOOSTING ANTITUBERCULOUS DRUGS TO IMPROVE TREATMENT COMPLIANCE

Alain Baulard, Institut Pasteur de Lille, France

Side effects associated with tuberculosis therapy lead patients to non-compliance, and subsequently to the emergence of drug resistance. Increasing the therapeutic index of anti-TB drugs should thus improve treatment effectiveness.

Ethionamide (ETH) is a very efficient antituberculous prodrug but has a relatively low therapeutic index. The biochemical activation of ETH by mycobacteria is catalyzed by the Bayer-Villiger monooxygenase EthA. The transcription of *ethA* is under the control of the transcriptionnal regulator EthR. We have shown that the genetic inactivation of *ethR* in *M. bovis* BCG leads to a dramatic increase of sensitivity to ETH, demonstrating the contribution of EthR to some innate resistance of mycobacteria to this antibiotic.

We then embarked on experiments to identify chemical compounds able to interfere with the repressor function of EthR. Recently solved crystallographic structures of EthR allowed designing a pharmacophoric model of inhibitors. A series of molecules fitting to this model was selected and screened for their capacity to inhibit the EthR-DNA interaction. Hits were cocrystallized with EthR and the structures were used to drive the synthesis of analogs. This approach allowed for the identification of potent EthR inhibitors that lead to a drastic reduction of the therapeutic dose of ETH. We propose that such antibacterial synergism might even permit to reconsider the use of ETH as a first line therapy.

UNDERSTANDING THE EVOLUTIONARY SUCCESS OF THE TB BACILLUS A COMPARATIVE APPROACH

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Tubercle bacilli have traditionally been seen as highly homogenous organisms, reflecting the restricted genetic variation and the clonal population structure of the *Mycobacterium tuberculosis* complex (MTBC). This situation has been reconsidered since our recent description of 9 groups of rare human TB clinical isolates from East-Africa with unusual smooth colony morphology (smooth MTB). These isolates, which include *M. canettii* strains, share many properties of MTBC members, but radically differ in terms of a more diversified population structure and obvious traces of horizontal gene transfer (HGT). These features suggest that the smooth MTBs are extant representatives of a much broader and older progenitor species, named *M. prototuberculosis*.

Multi-locus sequence typing of 16 house-keeping genes of an extended collection of 56 smooth MTB strains revealed the existence of at least 5 novel groups. Together with polymorphisms in intein-encoding sequences, this analysis further demonstrates the large genetic diversity of the tubercle bacilli and suggests that the MTBC is a particularly succesful clonal lineage that has emerged from the *M. prototuberculosis* progenitor pool, probably involving HGT episodes (clonal epidemic structure). Therefore, whole-genome sequences from the 4 most genetically distant smooth MTB strains are being determined using a combination of Sanger-, 454- and Illumina-based technologies. Preliminary analyses indicate extensive chromosomal rearrangements and the existence of multiple genomic islands compared to MTBC genomes. Together with studies on the biological properties, comparative and functional genomic studies of smooth MTB thus have the potential to identify the factors that have led to the predominance of *M. tuberculosis* as a human pathogen.

FLU, AVIAN FLU AND EMERGING ASPECTS (H1N1 RESISTANCE)

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Influenza viruses are characterized by a high genetic diversity, specially regarding the two viral glycoproteins hemagglutinin (HA) and neuraminidase (NA). Many virulence factors have been identified and HA gene sequence is one of them, regarding species specificity (affinity to α 2-3 or α 2-6 receptors) and virulence (polybasic cleavage site). H5N1 human cases present specific clinical settings, especially regarding high mortality rate (60%), associated with digestive symptoms and non-controlled viral dissemination.
Neuraminidase inhibitors are increasingly used to treat influenza infections and a major concern has emerged last winter (2007-2008) with an important diffusion of A H1N1 viruses resistant to oseltamivir, harboring a H275Y mutation on NA. The emergence of these resistant viruses appears to be unrelated to any selective pressure of antiviral drugs and highlights the major role of influenza surveillance networks.

CIRCULATION OF INFLUENZA VIRUSES IN NORTHERN EURASIA – GLOBAL CONSEQUENCES (ECOLOGY, EVOLUTION, DRUG RESISTANCE, VIRULENCE).

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In natural ecosystems of N. Eurasia were isolated about 1000 strains of H1 – H14 (N1 – N9) influenza viruses including 56 strains of H5 deposited into State Virus Collection. Evolution of HPAI H5N1 virus (clade 2.2.) splashed from Qinghai (China) to W. Siberian natural ecosystems (July 2005) and penetrated by autumn birds migration to Europe, Africa, S.W. Asia was analyzed (2005-2008).

Strains from wild birds and poultry (July–November 2005; June 2006; February, September, December 2007; April 2008) were completely sequenced. Obtained data showed extensive genes exchange among viruses through avian migration routs from N. Eurasia to S.-E. Asia. Unique aminoacid substitutions in PB2, PB1, PA, HA, NP, M2 correlated with substantial decreasing of virulence (for period 2003-2008). Mass infection of not only aquatic long-distance migrants, but also terrestrial short-distance migrants was revealed. In natural ecosystems of Northern Eurasia two HPAI genotypes circulate now: western (starting 2005) – 2.2 two clasters; eastern (starting 2008) – 2.3.2.

Panel of MAB received to H5N1 viruses proteins. About 1000 epidemic strains (5 linages H3N2, 3 linages H1N1, 4 linages B) isolated. Resistance of H1N1, H3N2 to remantadine and oseltamivir evaluated.

MOLECULAR EPIDEMIOLOGY OF INFLUENZA VIRUSES IN RUSSIA IN 2005-2008. DEVELOPMENT OF NEW INFLUENZA VACCINES

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Influenza epidemics in Russia occur virtually every year being determined by continuous variability of modern influenza A and B viruses. Research Institute of Influenza, RAMS and its 49 basic laboratories isolated more than 500 influenza A and B virus strains on the territory of Russia every year.

Epidemic events in Russia in 2007-2008 were characterized by more intensive circulation of influenza A H1N1 viruses. Strains of this epidemic season were closely related to the last reference strain A/Brisbane/59/07. Most analyzed H1N1 2007-2008 isolates were not direct evolutionary continuation of 2005-2007 viruses and could be separated out in an independent group with a certain set of amino acid substitutions in HA1. Comparative analysis of these strains with vaccine and previous Russian strains showed the differences in 6 amino acids from A/New Caledonia/20/99, 5 amino acids from A/Solomon Islands/3/06, 1 amino acid from A/Brisbane/59/07 and 8 amino acids from Russian strains isolated in 2006-2007.

Phylogenetic analysis of haemagglutinin gene of Russian H3N2 isolates has shown that all the 2008 isolates studied are genetically close to the new reference influenza virus strain A/Brisbane/10/2007. The majority of 2008 isolates clusterizes in an evolutionary group different from 2006-2007 isolates with 2 amino acid changes in HA1. Comparative analysis of these strains with vaccine strains and epidemic strains isolated during previous years revealed differences in 2-6 amino acid positions.

Phylogenetic analyses of influenza B virus strains demonstrated co-circulation of 2 lineages – Yamagata and Victorian – on the territory of Russia. However it must be noted that every year we observed the “switching” of the dominating lineage. In 2006-2007 epidemic season it was Victorian line that prevailed and in 2007-2008 it was Yamagata line.

Long-term monitoring showed that accumulation of point mutations in HA and NA genes led to the shift of epidemically urgent influenza A and B virus variants. Influenza viruses often evolve in the so called “silent way” when mutations in HA gene do not manifest until their accumulation does not lead to the appearance of the virus with antigenic and genetic features optimal for epidemic prevalence. Such evolutionary route could be traced in appearance of the new antigenic variant A/Brisbane/59/07 (H1N1).

Besides the antigenic evolution genetic changes include mutations that lead to appearance of drug resistance. Molecular analysis revealed that about 40% of strains among analyzed 2008 Russian isolates A(H1N1) have tyrosine instead of histidine at residue 275. This substitution leads to ozeltamivir resistance. The number of ozeltamivir resistant strains in Saint Petersburg was much higher (92%). Interestingly that the mutation in M-gene of influenza A viruses resulting in rimantadine resistance was observed mainly in isolates of H3N2 subtype and never in strains that were resistant to ozeltamivir.

We are working on recognition of new subtypes of influenza A virus in human and avian populations, identification of prototype vaccine strains with the desired antigen properties for use as animal and human vaccines, selection of new type and subtype specific antigenic determinants for development of highly sensitive diagnostic systems.
NS-gene could be the most interesting in respect of the development of new vaccines.
Design of novel vaccines based on NS1-deletion technologies, replication defective vaccines is an important step ahead to safe vaccines that lost internal features of pathogenicity. AVIR Green Hills Biotechnology Research Development and Institute of Influenza has developed a replication-deficient influenza vaccine virus that lacks the NS1 gene (ΔNS1). This vaccine was generated by reverse genetics and is applied intranasally. It combines the advantages of live and inactivated vaccines. The lack of the NS1 gene and absence of replication renders this novel vaccine as safe as conventional killed vaccines.

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