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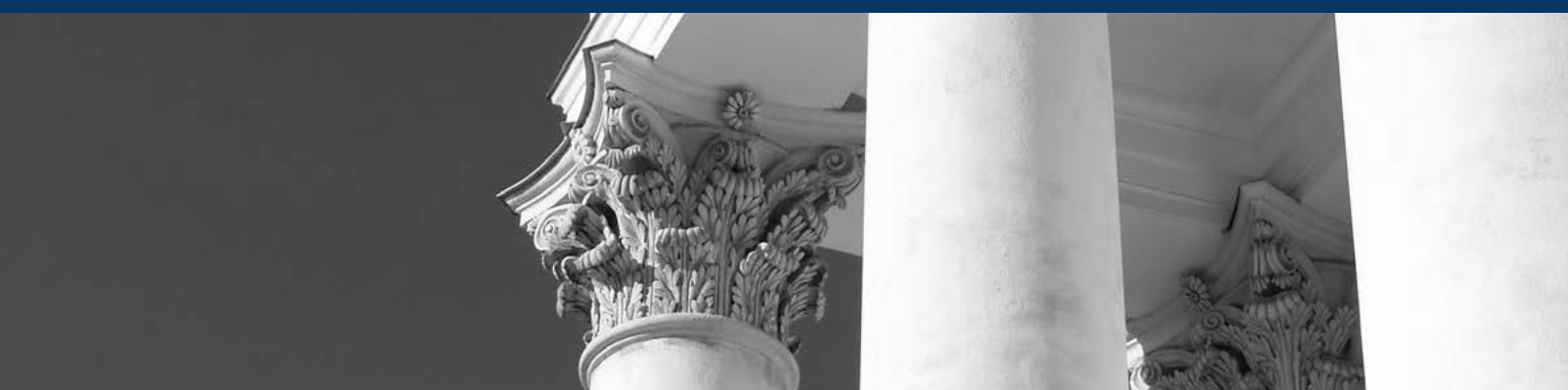
IULIU HAȚIEGANU
UNIVERSITY OF
MEDICINE AND PHARMACY
CLUJ-NAPOCA

"IULIU HATIEGANU" UNIVERSITY OF MEDICINE AND PHARMACY DOCTORAL SCHOOL

NEUROSCIENCE

PROGRAM

2015-2016 | SECTION 2 | MARCH 24TH - 25TH, 2016



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Michael Chopp

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Anca Buzoianu /Romania
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INTERNATIONAL GUEST LECTURERS

MICHAEL CHOPP
USA

Michael Chopp, PhD, is Vice Chairman for Research of the Department of Neurology, Scientific Director of the Henry Ford Neuroscience Institute, and is the Zoltan J. Kovacs Chair in Neuroscience Research. He is also Distinguished Professor of Physics at Oakland University.

He received his MS and doctorate degrees in Mathematical and Solid State Physics from New York University. After nearly 10 years of working as a Physicist and as a Professor of Physics, Dr. Chopp made a career change and turned his interest to translational research in neuroscience Dr. Chopp's research has primarily focused on: 1) cellular and molecular biology of ischemic cell injury, 2) the pathophysiology of stroke, traumatic brain injury, peripheral neuropathy, multiple sclerosis, and glioma, 3) combination thrombolytic and neuro and vascular protective therapies for stroke, 4) mechanisms of neuroprotection, 5) cell-based and pharmacological neurorestorative therapies for stroke, traumatic brain restorative therapies for stroke, traumatic brain injury and neurodegenerative disease, 6) molecular and cellular mechanisms underlying neurogenesis and angiogenesis and the induction of brain plasticity leading to functional and behavioral recovery after neural injury,7) treatment of glioma and breast cancer, 8) exosomes/microRNA for treatment of neurological injury and disease, and 9) magnetic resonance imaging. Dr. Chopp has 639 peer reviewed publications, ~ 50 book chapters and has given 430 plenary lectures and invited presentations. He has chaired National Institutes of Health (NIH) study sections and has often served as a consultant to government agencies, the U.S. National Institutes of Health, and the pharmaceutical industry.

Awards include:

2001 Top Ten Research Advances of 2001, "Treatment of Stroke with Bone Marrow Stromal Cells", American Heart Association

2005 Distinguished Scientist Award, Henry Ford Medical Group, Board of Governors

2012 Lecture of Excellence and World Stroke Organization (WSO) Award, Remodeling and rewiring the intact CNS as a treatment for Stroke, 8th World Stroke Congress, Brasilia, Brazil, October

2014 Abraham White Distinguished Science Award. "For discovery of the role of thymosin beta 4 in the treatment of brain injuries and neurodegenerative diseases; 4th International Symposium on Thymosins in Health and Disease, Washington, DC, October

2015 Thomas Willis Lecture Award, International Stroke Conference, Nashville, TN, February

MAURIZIO LEONE
ITALY

Medical degree at the University of Torino in 1980. Resident at the Clinica Neurologica of the same University and the Epidemiological Unit of the Torino Health Authority from 1981 to 1986. Board Certification in Neurology in 1984 and in Clinical Neurophysiology in 1991. Guest Researcher at the Neuroepidemiology, Branch, NINCDS, NIH, Bethesda, USA (1986-7). After 1987 he has worked in the Departments of Neurology of several hospitals of North Italy (Ivrea, Aosta, Novara) as Senior Attendant. Head of the Multiple Sclerosis Centre at the University Hospital in Novara, 2002-14. Since September 2014 head of the Neurology Unit, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo. Consultant at the Laboratorio di Neurologia, "Mario Negri" Pharmacological Institute in Milan (1998-2014). Teacher of Neurology (Nursing School 1998-2013, School of radiology technicians 2010-3) and of Emergency Neurology (Residency in neurology 1999-2008), University of Piemonte Orientale, Novara. Within the European Academy of Neurology he is Chair of the Scientific Panel "Neurotoxicology", member of the Scientific Committee and of the guideline production group, and member of the assembly of delegates. President of the Italian Society of Neuroepidemiology (2012-4), member of the Italian Society of Neurology, and New York Academy of Sciences, honorary member of the Moldovan Society of Neurologists. Associate Editor of European Journal of Neurology since 2006; referee for many neurological journals. Research area is neuroepidemiology -including amyotrophic lateral sclerosis, multiple sclerosis, alcoholism and epilepsy-, and evidence-based neurology. He is author of 157 papers in peer-reviewed journals.

MAURA PUGLIATTI
ITALY

Maura PUGLIATTI, MD, PhD is Associate Professor of Neurology at the University of Ferrara, Italy. She took a PhD in 2007 and was a Research Fellow in 2007-10 at the Dept. of Public Health and Primary Health Care, University of Bergen, Norway, actively coordinating a large multi-center case-control study on multiple sclerosis (MS) and environmental risk factors. She has been Visiting Professor at the University of Bergen (Erasmus Teaching Staff Mobility program to medical students, 2010-12), University of Belgrade, Serbia (to PhD student, 2015). Since 2011 she is Adjunct Professor at the Dept. of Clinical Medicine, McGill University, Montreal, Canada within collaborative research in MS epidemiology. In 2008-14 she was Chair of the EFNS Scientist Panel of Neuroepidemiology and Public Health, and she co-chairs the same Panel for the European Academy of Neurology. Her main research areas in epidemiology are MS, epilepsy, amyotrophic lateral sclerosis and myasthenia gravis, through collaborative research at national and international level. She is author of 111 papers in peer-reviewed scientific journals.

JOHANNES VESTER
GERMANY

Born, 1952, he specialized in Veterinary Medicine between 1971 and 1974 at the University in Munich, then changed to the University in Cologne in 1974 and specialized in Human Medicine from 1974 to 1980. In 1976 to 1979, he also studied biometric methods for pharmacology and clinical research at the Institute for Data Analysis and Study Planning in Munich.

While studying human medicine, he completed research work on pattern recognition in the visual brain and developed a pharmacodynamic Neuron Simulation Model at the Institute for Medical Documentation and Statistics of the University at Cologne. From 1985 to 1995, he was member of the Ultrahigh Dexamethasone Head Injury Study Group and leading biometrician of the German GUDHIS Study.

Since 1982 has been holding advanced training courses on biometry for professionals in clinical research and university establishments.

Since 1995 he is Senior Consultant for Biometry & Clinical Research. He planned and evaluated about 150 randomized clinical studies worldwide and is member of various international Advisory Boards and Steering Committees including participation as biometric expert in regulatory authority panels and in FDA, EMEA, and BfArM hearings. He is also elected fellow in international scientific organizations and statistical peer reviewer in leading medical journals.

COURSE PROGRAM

COURSE PROGRAM

MARCH 24TH, 2016

"MULTIMEDIA" AUDITORIUM, "IULIU HATIEGANU" UMF CLUJ-NAPOCA

8 VICTOR BABES STREET | CLUJ-NAPOCA | ROMANIA

09:00 – 09:10	Dafin F. Muresanu /Romania Introduction to the concept of International Doctoral School Neuroscience Program
09:10 – 10:20	Michael Chopp /USA Exosomes/miRNA as nano-neurological therapy mediate recovery after stroke and neural injury
10:20 – 11:10	Michael Chopp /USA The diabetic brain-pre and post stroke
11:10 – 12:00	Michael Chopp /USA Treatment and remodeling of white matter in models of multiple sclerosis and peripheral neuropathy
12:00 – 12:30	Coffee Break
12:30 – 13:15	Maura Pugliatti /Italy Population Surveys: scopes, prevalence, incidence, health registries
13:15 – 14:00	Maura Pugliatti /Italy Population Surveys: methodological problems, standardization
14:00 – 15:00	Lunch Break

MARCH 24TH, 2016

"MULTIMEDIA" AUDITORIUM, "IULIU HATIEGANU" UMF CLUJ-NAPOCA
8 VICTOR BABES STREET | CLUJ-NAPOCA | ROMANIA

15:00 – 15:45	Maura Pugliatti /Italy Cohort Studies
15:45 – 16:30	Maura Pugliatti /Italy Case-control Studies, confounding, effect modification and interaction
16:30 – 17:00	Coffee Break
17:00 – 18:00	Maura Pugliatti /Italy Descriptive epidemiology: article reading and exercise on standardization – discussions, practical examples
18:00 – 19:00	Maura Pugliatti /Italy Case-control studies: article reading – discussions, practical examples

COURSE PROGRAM

MARCH 25TH, 2016

"MULTIMEDIA" AUDITORIUM, "IULIU HATIEGANU" UMF CLUJ-NAPOCA

8 VICTOR BABES STREET | CLUJ-NAPOCA | ROMANIA

09:00 – 09:45	Maurizio Leone /Italy Study design
09:45 – 10:30	Maurizio Leone /Italy Sources
10:30 – 11:00	Coffee Break
11:00 – 11:45	Maurizio Leone /Italy Clinical trials: planning and conduction
11:45 – 12:30	Maurizio Leone /Italy Clinical trials: analysis of results
12:30 – 13:30	Lunch Break
13:30 – 14:30	Maurizio Leone /Italy Clinical trials: writing a research protocol – discussions, practical examples
14:30 – 15:30	Maurizio Leone /Italy Clinical trials: article reading – discussions, practical examples

MARCH 25TH, 2016

"MULTIMEDIA" AUDITORIUM, "IULIU HATIEGANU" UMF CLUJ-NAPOCA
8 VICTOR BABES STREET | CLUJ-NAPOCA | ROMANIA

15:30 – 16:00	Coffee Break
16:00 – 16:45	Johannes Vester /Germany Basic Understanding of Principle Biometric Features in Clinical Research
16:45 – 17:30	Johannes Vester /Germany Interpreting Meta-analyses within the Framework of Evidence-Based Medicine
17:30 – 18:15	Johannes Vester /Germany Evidence Based Medicine and the GRADE System
18:15 – 19:00	Johannes Vester /Germany The Importance of Quality Assurance

ABSTRACTS

EXOSOMES/MIRNA AS NANO-NEUROLOGICAL THERAPY MEDIATERECOVERY AFTER STROKE AND NEURAL INJURY

MICHAEL CHOPP
Oakland University, Rochester, USA

The ability to regulate and modulate intercellular communication may provide the basis for the treatment of neurological injury, neurodegenerative diseases and stroke. Exosomes are small (30-100 nm) endosomal generated particles consisting of a complex lipid membrane and contain proteins, RNAs, mRNAs and microRNAs (miRNAs). Nearly all cells generate exosomes, and these small lipid containers are ubiquitous in biological systems and provide an intercellular communications network which regulate cellular function. Exosomes mediate intercellular communication by transferring proteins, lipids, and genomic materials including mRNAs and miRNAs between source and target cells.

In this presentation, I will describe our work on the treatment of stroke, traumatic brain injury and diabetic peripheral neuropathy with exosomes, with a focus on the transfer of microRNA (miRNA) content within the exosomes to recipient cells. miRNAs are 20-25 nucleotide non coding RNA which regulate gene translation. They act as major molecular switches and are post transcriptional regulators of protein production, and they can simultaneously impact multiple molecular pathways and signaling within cells. We have found that cell-based therapies promote neurological recovery and promote neurovascular remodeling by transferring exosomes to recipient cells. Thus, we have harvested exosomes by means of ultracentrifugation or using biochemical methods from a variety of cells, and directly employed these exosomes by intravenous administration for stroke and TBI to promote neurological recovery. By labeling the exosomes with fluorescent markers we have shown that intravascular administration of these exosomes pass the blood brain barrier and enter into parenchyma cells. The content of these exosomes, as noted, consists of proteins, miRs and mRNAs. Downstream molecular targets of specific miRs known to be transferred into parenchyma cells have been shown to affect their molecular targets, thus demonstrating that the harvested exosomes transfer miRs to parenchyma cells and thereby affect the molecular downstream targets.

In vitro studies using microfluidic chambers can be employed to give insight into how exosomes promote neurological recovery. Microfluidic chambers are compartmental structures where neuronal soma and axons are located in separate compartments. The microfluidic device permits distal axons to grow into the axonal compartment after passing 450μm long microgrooves that connect the cell body and axonal compartments. We demonstrate that exosomes placed either on the somal or the axonal compartment significantly promote axonal outgrowth. This exosome enhanced outgrowth can also be inhibited by using siRNA to block Argonaut proteins, such as Ago2. Ago2 protein is a component of the RNA induced silencing complex (RISC), and is the key regulator of miRNA function by mediating the activity of miRNA-guided mRNA cleavage or translational inhibition. The majority of miRNAs in exosomes are bound to Ago2. Reduction of Ago2 in exosomes abolishes axonal outgrowth. Very importantly, the content of exosomes can be tailored to contain specific miRNAs. By transfecting exosomes source cells with specific genes or using siRNA on exosomal parental source cells, we can respectively, upregulate or reduce miRNA content within exosomes derived from parental cells. Using microfluidic chambers and vascular angiogenic experiments we demonstrated that targeting specific miRs will impact specific physiological events. For example, when parental mesenchymal stromal cells (MSCs) were transfected with a miR-17-92 cluster plasmid, exosomes harvested from the MSCs exhibited enriched levels of the miR-17-92 cluster. Applying these exosomes to either the somal or axonal compartments of the microfluidic chamber significantly increased neurite outgrowth. Thus, tailored exosomes can deliver their selective cargo miRNAs into and activate their target signals in recipient neurons.

We have performed extensive preclinical studies on the therapeutic use of exosomes for stroke, traumatic brain injury, diabetic peripheral neuropathy, multiple sclerosis and dementia. For example, our data demonstrate that treatment of embolic stroke with exosomes derived from MSCs or other progenitor cells one or more days after stroke onset significantly promotes neurological recovery compared to control populations. Treatment with exosomes also concomitantly enhanced neurovascular plasticity, promoted neurogenesis, angiogenesis, and oligodendrogenesis. Similarly, treatments of experimental traumatic brain injury, peripheral neuropathy, and neurodegenerative models using exosomes harvested from a variety of cells, as well as harvested exosomes tailored to contain specific miRs, were shown to enhance neurological recovery along with neurovascular plasticity. Thus, we are developing a novel therapy, nano-neurological therapy, utilizing the body`s nano-lipid containers, exosomes, which contain and can be loaded with proteins, miRs and genetic instructions, to promote neurological recovery.

THE DIABETIC BRAIN-PRE AND POST STROKE

MICHAEL CHOPP
Oakland University, Rochester, USA

Fully one-third of stroke patients are diabetic and diabetes, both type 1 and type 2, impact affect millions of people worldwide. This presentation will be divided into three major components: 1) The effect of diabetes on the non-stroke brain- Here, I will focus on the impact of diabetes on cognition and learning in the aging brain. From experimental models, I will demonstrate, particularly in Type 2 models of diabetes, that there is substantial impairment of cognitive and learning in the aging animals. To obtain insight into the mechanisms responsible for this impairment, I will discuss the glymphatic system, the means by which the brain eliminates toxic metabolites, and will show that the glymphatic system in the aging diabetic brain is compromised and the impairment of this system significantly correlates with cognitive dysfunction . Mechanisms underlying and contributing to glymphatic impairment will be discussed. Importantly, I will demonstrate the feasibility of potentially non-invasive monitoring the status of the glymphatic system. 2)The effect of diabetes on stroke-Using experimental models, I will demonstrate that diabetes exacerbates neurovascular pathology and functional outcome after stroke. Angiopoeitin 1 (Ang1)will be shown to play a pivotal role in mediating neurovascular status after stroke. Diabetes will be shown to reduce Ang1. Ang 1 enhances neurovascular function, including angiogenesis, stabilizes the blood brain barrier and promotes neurite outgrowth. Diabetes will be shown to significantly reduce levels of Ang 1 and to increase its competitive binding protein Ang2, thus leading to worse neurological outcome post stroke. 3) The impact of diabetes on therapies for stroke will be discussed. In experimental models of embolic stroke, I will show that diabetes has an adverse effect on thrombolysis with recombinant tissue plasminogen activator (tPA) , promoting inflammation and BBB dysfunction. The effects of diabetes on neurorestorative therapies will be briefly described, demonstrating that early , 1 day , treatment of stroke with mesenchymal stem cells (MSCs) , fails to enhance recovery post stroke and may exacerbate brain damage and recovery. Treatment with cell-based therapies, at later time points, e.g. 3 days post stroke, however, may still promote neurological recovery in the diabetic animal. Interestingly, the late treatment of diabetic stroke with stem cells, may also provide a therapeutic effect via Ang 1. The presentation on diabetic stroke will end with a discussion of the role of microRNAs in diabetes and diabetic stroke.

TREATMENT AND REMODELING OF WHITE MATTER IN MODELS OF MULTIPLE SCLEROSIS AND PERIPHERAL NEUROPATHY

MICHAEL CHOPP
Oakland University, Rochester, USA

White matter damage and dysfunction play an important role in aging, stroke, neural injury and neurodegenerative diseases. Here, I will give some examples of how we can treat neurodegenerative diseases of the central nervous system (CNS) such as MS and the peripheral nervous system (PNS), such as peripheral diabetic neuropathy. 1) First, I will focus on models of multiple sclerosis and demonstrate how specific microRNAs (miRs), such as miR-146a may be employed to promote remyelination in an EAE model of MS and in a model (Cuprizone)primary white matter toxicity. miRs are master molecular switches which can concurrently regulate the translation of many genes. Thus, a single miR may simultaneously impact many molecular processes. Here, I will demonstrate that miR-146a enhances oligodendrogenesis and reduces inflammation, affecting cytokine production , macrophage polarization and toll-like receptor activity. Treatment of EAE as well as Curprizone white matter toxicity with a miR-146a mimic promotes neurological function and concomitantly enhances remyelination. 2) The second part of my presentation will focus on the therapeutic aspects of phosphdiesterase 5 inhibbitors (PDE5) in ameliorating the effects of diabetic peripheral neuropathy. I will show that PDE5 inhibitors such as, sildenafil, significantly improve neurological function and enhance neurovascular and white matter remodeling in the diabetic animal.. Among the mechanisms of action which will be discussed, is that sildenafil enhances Angiopoietin1 expression in Schwann cells and in endothelial cells, as well as upregulates trophic factor expression. Thus, there are multiple ways to treat diseases both in the CNS and the PNS, with basic molecular means such as miRs as well as agents which may enhance expression of selective miRs (to be discussed in future lectures!!-love Cluj-Napoca and my wonderful colleagues))

STUDY DESIGN

MAURIZIO LEONE
University of Piemonte Orientale, Novara, Italy

This presentation will be a preliminary exploration of different study designs that will be deeper outlined in the following presentations. The choice of the study design has to be driven by a very clear research hypothesis that must always be clearly stated in the protocol of the study. The most usual study designs will be presented for observational as well experimental studies. Study designs will be placed in hierarchical order according to the pyramid of evidence (case reports and clinical series, cross sectional, case-control and cohort studies), and the strengths and weaknesses of each design will be stressed. Experimental studies will be discussed. Special emphasis will be given to studies for evaluating accuracy and reproducibility of diagnostic tests. Optimization of study design is a fundamental point to improve research, to avoid repeatability of studies and increase reproducibility of research.

SOURCES

MAURIZIO LEONE
University of Piemonte Orientale, Novara, Italy

This lecture will define the sources of data for different types of epidemiological studies in order to select the most appropriate types of information for a specific project. Sources of data are divided in current and ad-hoc sources. Several types of current data are available for epidemiologic studies: demographic data (censuses), vital registration systems (birth and death certificates), notification of infectious diseases, hospital admission/discharge archives, exemptions codes for specific diseases, drug prescriptions archive, reports of accidents at work, and reports of professional diseases. Ad hoc data are household samples, registers (specific disease or group of diseases), and clinical data banks. Aim of the lecture is to understand the advantages and disadvantages of different types of data sources, the importance of representativeness, the importance of evaluating the quality of data (completeness, accuracy, relevance and timeliness). Special focus will be given to the health information systems and their possible uses for epidemiologic studies. Examples from neurological studies will be offered.

CLINICAL TRIALS: PLANNING AND CONDUCTION

MAURIZIO LEONE
University of Piemonte Orientale, Novara, Italy

A brief history of clinical trials will introduce to the need of comparative assessment of treatments. The elements of the randomized clinical trial (RCT) will be explained. The RCT is an experiment done in clinical research aimed to answer questions about biomedical or behavioral interventions, including drugs, vaccines, medical devices, therapeutic strategies, and life-style choices. It must have internal and external validity. Internal validity includes the concepts of randomization (to prevent the selection bias), blindness of patient and operator (to prevent the performance bias), and blindness of outcomes evaluators (to prevent the detection bias). The importance of selecting outcomes will be outlined. External validity concerns the applicability of the results to the clinical practice, and the practical usefulness of results, based on the selection of outcomes with strong impact on the natural history of the disease. Clinical trials also generate data on safety. RCT will be classified according to the intervention (explanatory and pragmatic trials), the manner in which the participants are exposed (parallel arms, cross-over, factorial, N-of-1), the number of participants, the participants' and investigators' knowledge about the treatment (open, blinded), and the objective (superiority, equivalence, non-inferiority). Lastly, the stages of clinical trial research will be outlined. Crucial ethical issues will be dealt with in different parts of the lecture.

CLINICAL TRIALS: ANALYSIS OF RESULTS

MAURIZIO LEONE
University of Piemonte Orientale, Novara, Italy

A brief history of clinical trials will introduce to the need of comparative assessment of treatments. The elements of the randomized clinical trial (RCT) will be explained. The RCT is an experiment done in clinical research aimed to answer questions about biomedical or behavioral interventions, including drugs, vaccines, medical devices, therapeutic strategies, and life-style choices. It must have internal and external validity. Internal validity includes the concepts of randomization (to prevent the selection bias), blindness of patient and operator (to prevent the performance bias), and blindness of outcomes evaluators (to prevent the detection bias). The importance of selecting outcomes will be outlined. External validity concerns the applicability of the results to the clinical practice, and the practical usefulness of results, based on the selection of outcomes with strong impact on the natural history of the disease. Clinical trials also generate data on safety. RCT will be classified according to the intervention (explanatory and pragmatic trials), the manner in which the participants are exposed (parallel arms, cross-over, factorial, N-of-1), the number of participants, the participants' and investigators' knowledge about the treatment (open, blinded), and the objective (superiority, equivalence, non-inferiority). Lastly, the stages of clinical trial research will be outlined. Crucial ethical issues will be dealt with in different parts of the lecture.

EXERCISES:

CLINICAL TRIALS: WRITING A RESEARCH PROTOCOL

MAURIZIO LEONE
University of Piemonte Orientale, Novara, Italy

Writing a research protocol for an epidemiological study is a very challenging task, but is the prerequisite for a successful study. A carefully written protocol is the opportunity to explore any possible bias of the study, anticipate and prevent it from failure in collecting crucial information, guarantee methodological quality, evaluate feasibility and possible study impairments, lay down terms of reference for the collaborating partners, and allow for study reproducibility. Besides that, a good protocol is the basis for a good scientific paper. Students will be asked to design the protocol of a clinical trial, starting from their well-defined research question. The practical aspects of a protocol including background, objectives, methods of data collection and analysis will be outlined.

CLINICAL TRIALS: ARTICLE READING

MAURIZIO LEONE
University of Piemonte Orientale, Novara, Italy

A clinical trial will be suggested for critical appraisal. An evaluation grid will be provided to students, including several items for the evaluation of internal validity (randomization, blindness, outcomes) and external validity. Measures of effect size will be calculated. Evaluations by the students will be discussed point-by-point with the faculty, as well as the applicability of results to their clinical practice.

POPULATION SURVEYS: SCOPES, PREVALENCE, INCIDENCE, HEALTH REGISTRIES

MAURA PUGLIATTI
University of Ferrara, Italy

The lecture will provide an overview of the scope of population surveys particularly aimed at (i) setting the basis for developing research protocol of neuroepidemiological studies, and (ii) ensure a critical reading of the scientific literature on neuroepidemiological issues. The main measure in descriptive epidemiology will be elucidated, such as prevalence, incidence, mortality and the computation of corresponding epidemiological indices. An analysis of the main feature for such study designs will be discussed, among which the definition of a study versus source versus target population, the identification of 'outcomes' and 'exposures', the definition of cases, and identification of epidemiological sources for data collection (case ascertainment). Furthermore, genetic epidemiology and the study of familial aggregation will be discussed, as well as screening strategies for prevention and early treatment.

Examples of descriptive studies from specific neurological disorders, eg., migraine, epilepsy and seizures, cognitive impairment, amyotrophic lateral sclerosis, will be illustrated.

Lastly, the lecture will finally focus on data collection, databasing and disease registry, and how this approach for disease surveillance can indeed affect epidemiological estimates. Example of such registers and databases will be illustrated.

POPULATION SURVEYS: METHODOLOGICAL PROBLEMS, STANDARDIZATION

MAURA PUGLIATTI
University of Ferrara, Italy

This lecture will highlight the methodological problems when carrying out a population survey: the definition, measurement and distribution of disease determinants (putative risk/protective risk factors), the population structure, and the methods to standardize, directly or indirectly, study estimates to make them comparable. Example will be given from different chronic diseases.

COHORT STUDIES

MAURA PUGLIATTI
University of Ferrara, Italy

Besides descriptive studies, analytical epidemiological studies will be discussed during the course. These study designs imply a comparison group and the possibility to detect an association between an exposure and an outcome. Randomized clinical trials (RCTs) are experimental study designs wherein the investigator has the opportunity to administer a treatment or implement an intervention to different arms of study participants that have been randomized so as to minimize the risk of biases and equally distribute potential confounding.

Cohort studies imply instead the analysis of cohorts which have been 'naturally' selected by one or more exposure(s) and which are followed-up in time to assess the respective incidence of a disease.

These cohort may be prospective when the follow-up starts at the study time, and retrospective, when they have been defined in the past (by exposure, and not outcomes) for other purposes.

Exposures and outcomes will be discussed, as well as the computation of the measure of association, the relative risk or incidence rate ratio.

Advantages and disadvantages of cohort studies will be illustrated as well as criticalities, and examples from the clinical neurology provided.

CASE-CONTROL STUDIES, CONFOUNDING, EFFECT MODIFICATION AND INTERACTION

MAURA PUGLIATTI
University of Ferrara, Italy

Case-control studies stand lower in the analytical/observational study design hierarchy. Association between an outcome and the exposures are sought by comparing a group of cases and a group of controls who ideally belong to the same target population and who differ from cases for not having the disease.

Because cases and controls belong to an 'invisible' theoretical population cohort, which may not in truth overlap with the actual source population for both groups, such mismatch may overlook factors (confounders) which bias the results. Hence, how to select cases and controls to minimize bias (eg., by frequency or individual matching) and how to deal with potential confounding (eg., through randomization, restriction and stratification) will be illustrated. Effect modification and interaction will also be presented, as well as advantages and disadvantages of case-control studies.

DESCRIPTIVE EPIDEMIOLOGY: ARTICLE READING AND EXERCISE ON STANDARDIZATION - DISCUSSIONS, PRACTICAL EXAMPLES

MAURA PUGLIATTI
University of Ferrara, Italy

One or two articles from neuroepidemiological scientific literature (incidence, prevalence, mortality) will be selected. Students will be asked to go through critical reading with the support of an evaluation grid of items which should not be overlooked for good quality interpretations of results. Students will also be invited to suggest strategies to improve shortcomings when designing descriptive studies in neurology.

CASE-CONTROL STUDIES: ARTICLE READING - DISCUSSIONS, PRACTICAL EXAMPLES

MAURA PUGLIATTI
University of Ferrara, Italy

One or two articles from neuroepidemiological scientific literature (case-control studies) will be selected. Students will be asked to go through critical reading with the support of an evaluation grid of items which should not be overlooked for good quality interpretations of results. Students will also be invited to suggest strategies to improve shortcomings when designing case-control studies in neurology.

The primary goal of the teaching course is to provide non-statisticians with an basic understanding of the interconnections and relationships which are important in practice of Clinical Research and to improve the ability to implement and apply this basic knowledge in the proper interpretation of study results.

BASIC UNDERSTANDING OF PRINCIPLE BIOMETRIC FEATURES IN CLINICAL RESEARCH

JOHANNES VESTER
idv - Data Analysis and Study Planning, Germany

P-values, Effect Sizes and Confidence Intervals. Basic principles. Relationship with significance tests. Why confidence intervals rather than P-values? CONSORT requirements. Definition and handling in superiority and non-inferiority trials. Interpretation of the most common result situations. Examples from the literature. ICH and FDA approach.

INTERPRETING META-ANALYSES WITHIN THE FRAMEWORK OF EVIDENCE-BASED MEDICINE

JOHANNES VESTER
idv - Data Analysis and Study Planning, Germany

The role of meta-analyses within the framework of evidence-based medicine as keystones in the development of guidelines and therapy recommendations. Basic concept. How to read a forest-plot. Fixed and random effects. Measures of heterogeneity. Correct and false interpretation of meta-analyses through examples from the literature. Questions to be asked. Common traps.

EVIDENCE BASED MEDICINE AND THE GRADE SYSTEM

JOHANNES VESTER
idv - Data Analysis and Study Planning, Germany

Basic concept. From effect sizes to quality of evidence. Limitations of older systems & approaches. The Grading of Recommendations Assessment, Development and Evaluation. Key points of the GRADE system: imprecision, inconsistency, publication bias. Interpreting strength of recommendations. Examples from the literature.

THE IMPORTANCE OF QUALITY ASSURANCE

JOHANNES VESTER
idv - Data Analysis and Study Planning, Germany

Modern risk-based approaches and centralized statistical monitoring as basis for high precision RCTs. Why clinical trials fail. Practical examples from interactive study conduct control revealing common traps and problems in the conduct of clinical studies. New FDA and EMA approaches to ensure successful trials.