

**SCHOOL OF ADVANCED STUDIES- 2011 PhD Research topics**

Area of Studies

**LIFE SCIENCES AND PUBLIC HEALTH**

<b>Curriculum:</b>	<b>MOLECULAR BIOLOGY, BIOCHEMISTRY, AND BIOTECHNOLOGY</b>
<b>Learning objective</b>	<p>Synthesis and characterization of advanced materials for energetic electrochemistry. Synthesis and characterization of nanocompounds. Fundamental tools of reaction methodology to the construction of complex, polyfunctional molecules. Photocurrent generation from natural pigment doped electrodes. Research and development of environmentally friendly reagents. Studies on materials for the conservation of archaeological and art-historical artefacts. Chemical techniques of environmental control..</p>
	<p><b>Research topic n. 1: Dynamic aspects of translation initiation in bacteria and archaea</b></p> <p>The ribosome represents a universally conserved subcellular ribonucleoprotein organelle which plays an active role in determining the efficient and accurate translation of the genetic message into a protein product. Despite being the most complex ribozyme existing in nature, the ribosome is also the better understood macromolecular machinery from both the structural and functional points of view so that ribosomal research was and remains at the forefront of molecular biology studies. The dynamic aspects of the mechanism that ensures the correct selection of the translational start point of the messenger RNA by the ribosome is studied using a multidisciplinary approach that mainly focuses on fast kinetics analyses of the individual steps of the translation initiation pathway.</p>
	<p><b>Research topic n. 2: Prophages carrying virulence-resistance genes in group A streptococci and modifications to the bacterial genome upon lysogenization.</b></p> <p>Streptococcus pyogenes (GAS) is equipped with many virulence factors that have been categorized into two groups: prophage and chromosomally encoded. The phages are probably the most abundant form of life on the planet and are extremely flexible. Moreover they play a key role</p>

	<p>in bacterial genome diversification and gene acquisition as recently confirmed by the analysis of the numerous whole genome sequences available.</p> <p>In this context GAS represents a paradigm. The number of prophages within GAS genome is surprising, making it polylysogenic and providing about 50% of the expressed genetic material diversifying strains from one another. In recent years many studies focused on the molecular epidemiology of phage encoded virulence genes in clinical GAS population. Available data indicate that phages in general have a significant association with specific M-types and that the presence of some phages (and the associated virulence genes) markedly contribute to the pathogenicity of the carrying strain.</p> <p>Another important aspect of phage biology is the mechanism by which bacteria acquire resistance against viruses. It has been found the clustered regularly interspaced short palindromic repeat (CRISPR) regions are present in bacterial genomes, providing genetic information on previous prophage encounters. We aim to elucidate the fine structural features of some prophages carrying genes encoding well recognized virulence factors in a cohort of clinical emm89 strains that caused acute pharyngitis in humans. Then the complete sequence of an emm89 strain virtually devoid of prophages will be determined. By a thorough comparison of these two main set of data, we are aimed at obtaining fundamental information on the modifications that occur in the group A streptococcus genome upon lysogenization. This approach will also start to shed light on mechanisms and factors underlying immunity to viral superinfection in this species and how they are overcome in the polylysogenic strains. The last objective will be to study the role of the newly identified putative factors by means of a genetic approach.</p>
	<p><b>Research topic n. 3: DNA vaccination in breast cancer</b></p> <p>Vaccination with tumor antigens is an exciting new approach for the treatment of cancer, which aims to generate immune responses against tumors, without the side effects associated with many conventional therapies.</p>

	<p>Overexpression or mutation of p185 protein, encoded by the oncogene Her-2/neu, plays a pivotal role in the pathogenesis of several malignancies, especially breast and ovary tumors, and it is associated with a poor prognosis. Our studies are involved in the development of a DNA vaccine suitable for the prevention and therapy for Her-2/neu carcinomas. Our DNA vaccines will be finally tested in a human clinical trial (Project financed by Ministry of Public Health). Moreover we have recently generated a reporter mouse, transgenic for a splice variant of Her-2/neu, that could represent an excellent preclinical model in order to test new targeted therapeutics.</p>
	<p><b>Research topic n. 4: Regulation of virulence genes in bacteria</b></p> <p>The invasion of the host by a pathogenic micro-organism results in reprogramming the transcriptional activity, allowing bacteria to promptly adapt to changes of growth conditions related to the transition from a free-living to a host-associated state. Establishing of pathogenesis is governed by complicated regulatory circuits involving different factors as global and specific regulators, nucleoid-associated proteins and small non-coding RNAs. The predominant aim of this research line is to study these regulatory interplays, particularly, focusing on riboregulation. In fact, it is emerging that ncRNAs, besides general genes regulation, can also play a key role in controlling the expression of many virulence determinants or affect adaptive stress-responses, which are important for bacteria to survive into the host. The experimental approach adopted is typically molecular. In particular, we use the most common techniques in the study of nucleic acids-protein interaction and analysis of the RNA <i>in vivo</i> and transcribed/translated in <i>in vitro</i> purified systems.</p>
	<p><b>Research topic n. 5: Dendritic cell-based cancer vaccines in human clinical trials: from bedside to bench.</b></p> <p>Ex vivo generated dendritic cells (DC) are currently used as autologous vaccines for advanced cancer patients. However, in terms of clinical responses DC immunization only</p>

	<p>occasionally induces stable disease or regression of tumor metastases. As yet it is not known whether the suboptimal clinical responses observed have been caused by the vaccination itself, or whether they reflect patients with a better prognosis who are capable of an immunoresponses.</p> <p>Recent evidence has emerged for an important role of DC in immuno-vascular interactions that mediate tumor progression. Indeed the tumor setting might induce a DC phenotype that is doubly poorly immunogenic yet capable of promoting angiogenesis.</p> <p>The aim of the joint research between the Unit of Translational Biology (Unicam) and the Immunotherapy and Somatic Cell Therapy Unit (Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Forlì) is to analyze the potential of DC to trans-differentiate into endothelial-like cells in order to identify subgroups of patients who are mostly likely to benefit from therapeutic vaccination.</p> <p>The study is partially supported by Cisco System and the Charity Association Alleanza Contro il Cancro.</p>
	<p><b>Research topic n 6: Search and development of new genetic-based immunoadjuvants</b></p> <p>The primary objective of the Unit of Translational Biology is the development of DNA based vaccines for the treatment of cancer and infectious diseases. From the conception we have sought to increase the efficacy of DNA vaccines through the use of immunostimulatory gene adjuvants, which are aimed at not only increasing the overall breadth of the immuneresponse but also towards skewing the type of immuneresponse from B to T cell effectors.</p> <p>Indeed the protective capacity of many currently used vaccines is based on the induction of neutralizing antibodies, but many pathogenes have adapted themselves in different ways to escape antibody-based protection. Thus the addition of a T-cell based components to existing antibody-based regimes offers the opportunity of providing superior protection against disease for which conventional vaccines have failed so far.</p> <p>This project will be conducted in collaboration with groups located in the USA (Boston) and in Australia (Adelaide).</p>

**Research topic n 7: Group A streptococcus and its bacteriophages: from biology to therapy**

Bacteriophages plays a fundamental role in modeling bacterial population. In addition, phage acquisition is one of the most efficient mechanism of intra-species horizontal gene transfer among bacteria.

The group A streptococcus (GAS) pathogenesis is significantly owed to the expression of different virulence and resistance genes carried by phages. The aim of this research is to elucidate different aspects of bacteriophage biology in GAS: structural genetics, regulation of gene expression, evolution, diffusion, contribution to the pathogenicity of the host. All the results will be used to design possible novel phage-based therapeutic strategies against GAS infections.