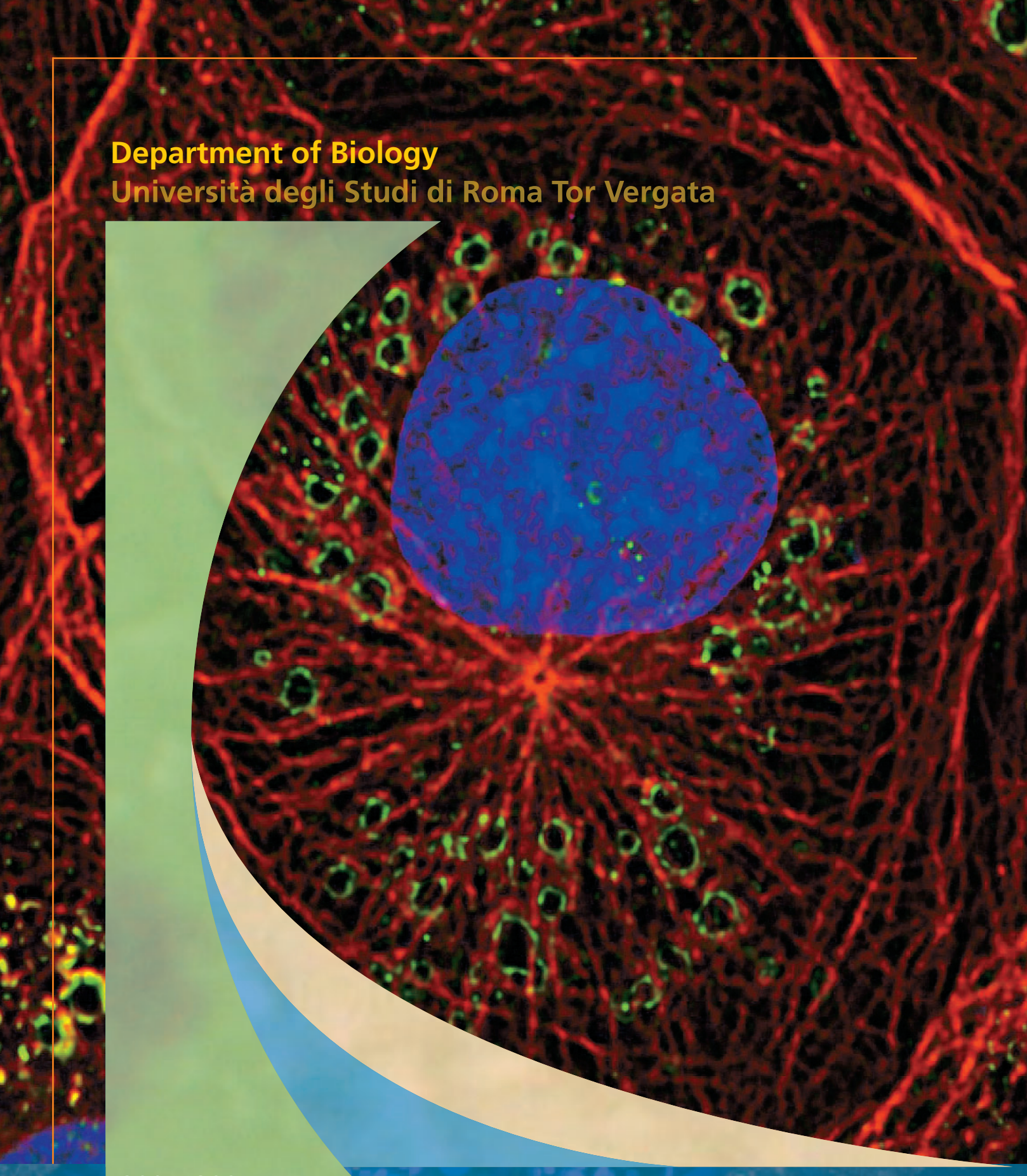

Department of Biology
Università degli Studi di Roma Tor Vergata

2005–2007
Scientific Report

ÈXÒRMA

Department of Biology Università degli Studi di Roma Tor Vergata

2005–2007
Scientific Report

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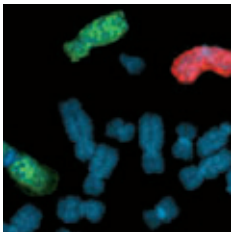
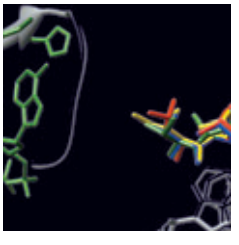
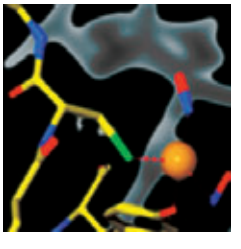
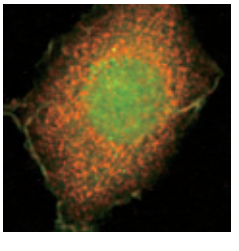
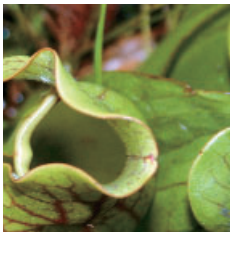
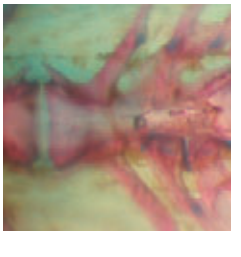

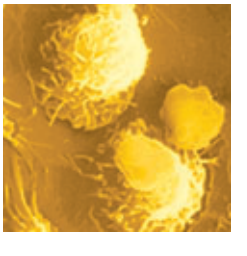


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Università degli Studi di Roma Tor Vergata

Scientific Report
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Introduction

The Biology Department is one of the most important in the Science Faculty of the University of Tor Vergata, due to the number of its researchers, the quality and productivity of its research laboratories and then the number of its trainee students, post-graduate students and research fellows.

The Department's main office is among the buildings of Via della Ricerca Scientifica. It occupies about 9400 square metres in area. The Biology Department also includes the Laboratory of Experimental Ecology and Aquaculture (LESA) in Via Cracovia and made up of the Ecology and Zoology groups, as well as owning "il Casale" (farmhouse) number 5 on the land belonging to the University Botanical Garden.

A key feature of this department is its multidisciplinariety, as is evident from the fact that nearly every field of biology is represented. Such a feature, which has allowed us to put in place a closely-linked network of department services and provides the opportunity for a continual sharing of skills and tasks, is the basis for development of research and for the provision of modern and multidisplinary methods of Biology teaching/learning. Its structure and organization demonstrate the great potential that can be generated when operating at the interface between various disciplines of modern biology.

The need to characterize and better define the biological processes in both a qualitative and quantitive way has led to the study of biodiversity using the very latest techniques of cytogenetics and molecular and cellular biology without ignoring field research and direct observation of animal and plant behaviour in relation to the surrounding environment or habitat.

In addition to the above, the fields of neurobiology and of biochemistry and then the study of nucleic acid regulation and large multimolecular complexes are also well-represented, thus guaranteeing the Department's contribution to making best use of the dramatic advances in the technology associated with the life sciences and, more generally, to scientific discoveries for the coming thirty years.

This combination of scientific and technological expertise has been confirmed by numerous acknowledgements and awards and by the high level of international publications such as in *Nature*, *Cell*, *Science*, all this in the space of the last three years, and then by both national and international funding for research.

The Department is also actively involved in recruiting young scientists as proven by the presence of a good number of research groups led by productive young researchers.

On behalf of all of our world-renowned scientists, outstanding research staff, and excellent administration, thank you for taking a few minutes to learn about our work and our organization.

Prof. Patrizia Aducci,
Chair of the Biology Department

An interview by Antonella Contaldo with Valerio Orlando*

Antonella Contaldo: I imagine any given person's prefessional life like a metre rule, one of those that you can open and close, as used in the hands of workmen and builders. I am convinced that a centimetre could be represented for some small job successfully carried out and then added on to the sum of those that came before it. You in the past were in the Biology Department of Tor Vergata, the second largest university in Rome, a place that I am sure leaves many memories for you, as you line them up, what are the best ones and what are the worst?

Valerio Orlando: I graduated from La Sapienza and in 1990 chose to study for a year as a post-graduate at the recently founded Tor Vergata. I was fascinated by the novelty and challenge of a newborn campus. In particular the new structure and projects that this new University had to offer. It had brand-new labs, implanting the surrounding countryside with a symmetry of massive squares, all smooth fresh concrete and multiple plate glass. And then there were already big-name teachers such as Prof. Amaldi and other up-and-coming ones like Prof. Cesareni. Everything was at the cutting edge, full of an enthusiasm that was infectious. I worked for a year in Prof. Paolozzi's lab alongside his team who were investigating specific aspects of the relationship between genome structure and function, a research area which still excites me and which I have been involved in throughout my professional career. I have very happy memories of it because the sense of enthusiasm was everywhere. I breathed it like air. I recall many friends collegues who started their successful career in Tor Vergata's Biology Department. At the end of that year (1990), with one of them, Andrea Musacchio, (currently at IFOM-IEO Campus in Milan), I left for Heidelberg. We hired a small van, we loaded it up with our dearest possessions including a Vespa and jar of rosemary, roman mint and basil and we set off for our new life. He stopped at EMBL Institute while my own chosen destination was the University in Heidelberg.

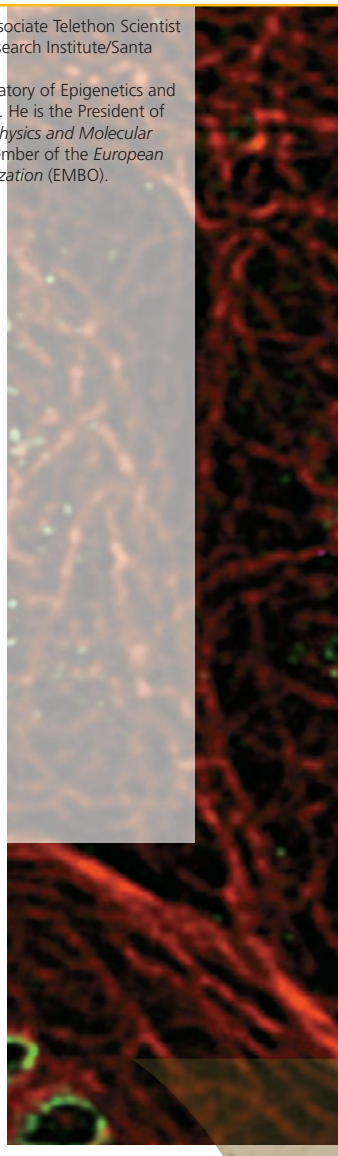
A.C.: But later you returned. Usually when you come back from a place that you have lived in, after being far away you weave a sort of screen of *nostalgia*, viewing things positively that might have been anything but and missing what might have vanished in your absence.

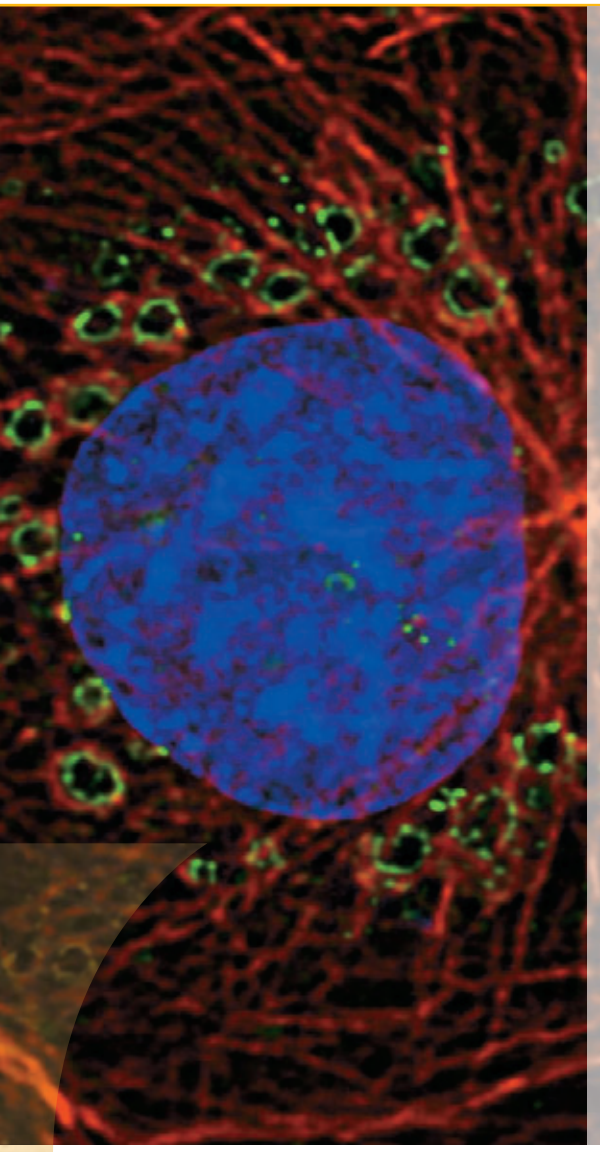
V.O.: Tor Vergata's Biology Department was certainly an important stage in my professional life, as there I met key people who gave me the right jump-start for, but it is also true that I stayed there only a year. Normally, when I come back to a place, I do not go to any great lengths to seek out or recreate in my memory what I have left behind. I prefer to concentrate on the changes, the dynamic aspects, taking them as they are.

A.C.: Zoology, Biochemistry, Development, Anthropology and so on, the Biology Department has changed its make-up a lot over the years. Having more disciplines, is this a weakness or a strength? Who are the respective losers and winners?

V.O.: To build a wide-based department, which brings and hold together disciplines which tend to exist in isolation is without doubt something to be valued, if not unique. To combine different disciplines also requires a lot of

*Valerio Orlando is an Associate Telethon Scientist at the European Brain Research Institute/Santa Lucia Foundation, Rome where he leads the Laboratory of Epigenetics and Genome Reprogramming. He is the President of the *Italian Society of Biophysics and Molecular Biology* (SIBBM) and a member of the *European Molecular Biology Organization* (EMBO).





co-ordination skills and vision. I find this feature of Tor Vergata's Biology Department as an exciting opportunity.

A.C.: For a department structured in this way to be competitive, how must one proceed so as not to lag behind, and who are the key players?

V.O.: This is exactly today's challenge but also fun. You must continue to open up to the world outside, and not remain staring at your own navel.
Today's world demands openness. The post-graduate programmes must throw down challenges and not fear comparison with the programmes proposed by the international scientific community. Attracting young, enthusiastic and talented people from all over the world, should be the goal. The quality is already very high.

A.C.: Public expense, money that fails to arrive, the inevitable cuts. "Let's tighten our belts", "We will row against the tide", phrases which we repeat daily like a sort of alarm-clock of another day worse than the one that came before. There is the world financial crisis and now universities seem to be in the firing line, paying the price. How do you go about honouring your work commitments if all this negative input deprives you of the peace of mind necessary to carry on going forward?

V.O.: I think negative inputs and attitudes have to be fought at all times. Promoting positive culture among the Colleagues and give the best example to young researchers is mandatory. Ethically speaking, I feel as a matter of urgency to take more responsibility towards my work, my Colleagues and my Organization and I do everything I can also to open up to the world outside to find inspiration. The way out from crisis always requires more creativity.

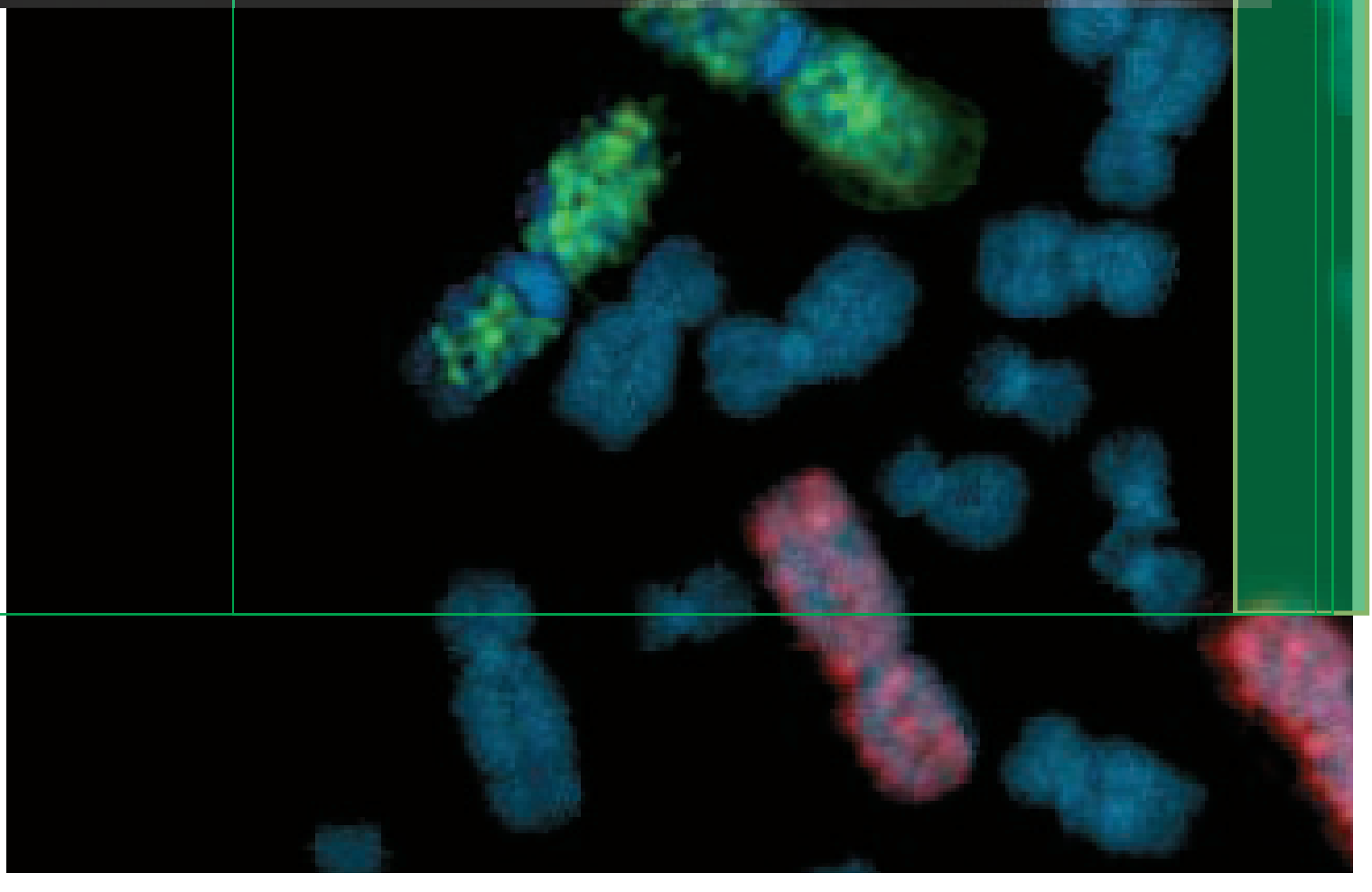
A.C.: Tor Vergata's Biology Department has any number of reasons for continuing its work, but I would like you to cite one in particular as to why we should continue to put our trust in Italian research.

V.O.: The Biology Department operates in a university context that is very broad; in being Rome's second university it is in a favourable position as regards other universities. This is itself is a reason to instil confidence.
And the Department is based on solid projects with a unique multidisciplinary environment. A treasure of human resources and skills that would deserve immediate investments.
The most urgent need is to set in motion the funding process and to win back the trust of young people, not just Italian young people but of those from abroad as well. Foreign students do not choose our Universities because they do not offer them equal opportunities. Their Italian colleagues seem to have lost motivation for the same reason. It is necessary to give young people a future back. Only when you have a concrete and positive idea of future ahead of you, can you devote yourself to achieving your dreams and projects and everything that should make life for all of a wonderful voyage of discovery. Indeed, discovery is our job: so they say.

Chapter one

Genetics

and Molecular Biology



GROUP LEADERS Francesco Amaldi • Fabrizio Loreni ■ **POST-DOC** Sara Caldarola ■ **PHD STUDENTS** Maria Chiara De Stefano • Valentina Iadevaia ■ **TECHNICAL ASSISTANT** Marcello Giorgi

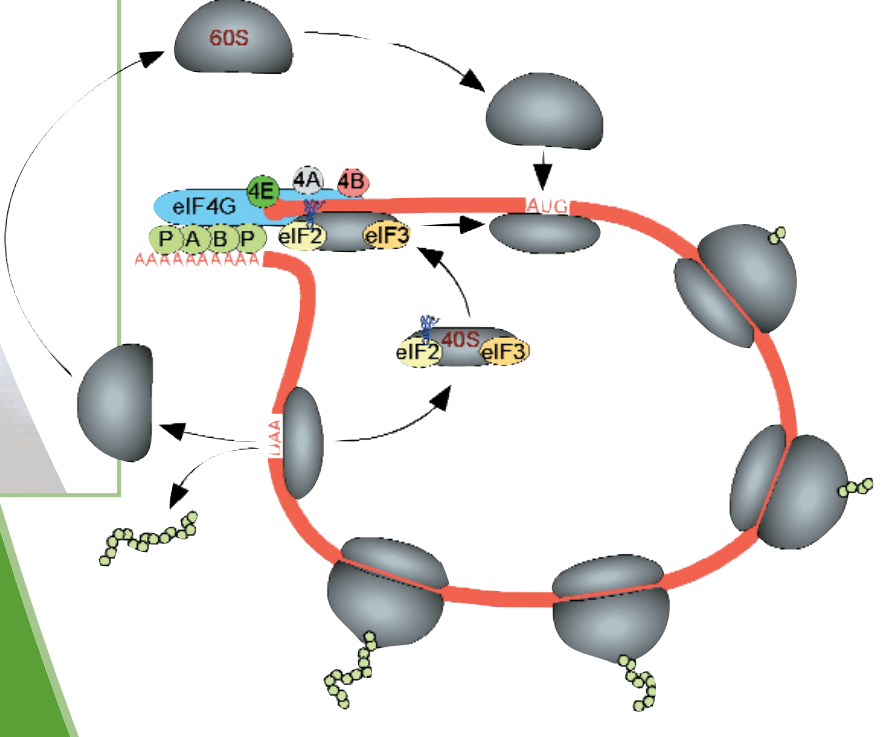
Regulation of gene activity at the translational level: the case of the TOP genes

Gorrini C., Loreni F., Gandin V., Sala L.A., Sonenberg N., Marchisio P.C. and Biffo S. 2005. Fibronectin controls cap-dependent translation through beta1 integrin and eukaryotic initiation factors 4 and 2 coordinated pathways. Proc Natl Acad Sci U S A 102, 9200-9205.

Ledda M., Di Croce M., Bedini B., Wannenes F., Corvaro M., Boyl P.P., Caldarola S., Loreni F. and Amaldi F. 2005. Effect of 3'UTR length on the translational regulation of 5'-terminal oligopyrimidine mRNAs. Gene 344, 213-220.

Loreni F., Iadevaia V., Tino E., Caldarola S. and Amaldi F. 2005. RACK1 mRNA translation is regulated via a rapamycin-sensitive pathway and coordinated with ribosomal protein synthesis. FEBS Lett 579, 5517-5520.

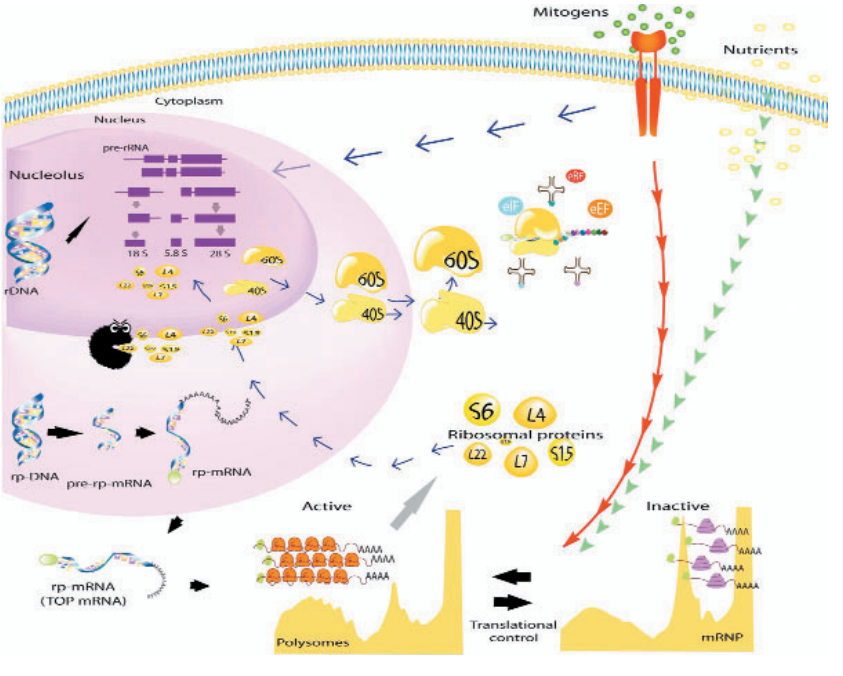
The long term research project of our group is directed at understanding the molecular mechanisms underlying the control of gene activity at the post-transcriptional level, mainly at the translation level. We are focusing on the class of TOP genes which includes more than 100 genes coding for ribosomal proteins and other products implicated in the production and function of the translational apparatus. All these genes are characterized by a typical short 5'UTR initiating with a sequence of 6-12 pyrimidines (Terminal OligoPyrimidine = TOP). This characteristic 5'UTR is involved in a "growth-associated" translational regulation typical of TOP genes. To better characterize this class of genes we investigated the structure and regulation of potential new TOP genes. An example is the case of RACK1, a protein that plays a central role in cell growth regulation. We analyzed RACK1 mRNA structure and expression showing that it has a 5' TOP sequence and that its translation is dependent on the availability of serum and amino acids in exactly the same way as TOP mRNAs (Loreni et al., 2005).
In the study on the cis-acting sequences involved in TOP mRNA translational regulation, we have analyzed the possible implication of the 3'UTR. In fact we have noticed that, besides the typical 5'TOP sequence, TOP genes are also characterized by very short 3'UTR, much shorter than most cellular mRNAs. The results indicate that, while TOP mRNA translational activity depends mostly on the 5'UTR, the short size of the 3'UTR contributes to the strinagency of regulation (Ledda et al., 2005).
Adhesion to fibronectin (FN), a major matrix protein involved in multiple processes, triggers translation activation through the coordinated regulation of initiation factors eIF4F and eIF2. We have also investigated the role of cell adhesion on the translation of TOP mRNAs. We were able to show that FN-dependent translation stimulation, unlike growth factor-stimulated translation, does not lead to increased TOP mRNA translation (Gorrini et al., 2005).



GROUP LEADER Fabrizio Loreni ■ **POST-DOC** Sara Caldarola ■ **PHD STUDENTS** Mara Angelini • Laura Biondini
■ **TECHNICAL ASSISTANT** Marcello Giorgi

Alteration of ribosome biosynthesis in human pathologies

Our research is focused on the molecular mechanisms underlying the regulation of the synthesis, function and metabolism of the ribosome in vertebrate cells.
Diamond-Blackfan anemia (DBA) is the first human disease associated to mutations in ribosomal structural protein. In fact, ribosomal protein (RP) S19 is mutated in about 25% of patients, whereas another 10% show mutations in RPS24, RPS17, RPL35A, RPL11, and RPL5. The major clinical feature of DBA is a congenital erythroblastopenia but approximately 30% of affected children present a variety of associated physical anomalies.
It is not clear how alterations in the synthesis and/or function of a ribosomal protein could influence normal development. To understand this point we searched for proteins interacting with RPS19 (Orru et al., 2007). We found that RPS19 binds PIM-1, an ubiquitous serine-threonine kinase whose expression can be induced in erythropoietic cells by several growth factors, such as erythropoietin (Chiocchetti et al., 2005).
Studying the alteration induced by mutations in RPS19 gene we showed that RPS19 mRNAs with mutations which introduce premature stop codons or eliminate them are rapidly turned over by the surveillance mechanisms, possibly causing a decrease in the RPS19 protein level. Less clear is the effect of missense mutations in RPS19. Our analysis of the functional properties of mutated RPS19 (Angelini et al., 2007) showed that RPS19 mutations can be grouped into two classes:
a) mutations that affect a very early step in ribosome biogenesis causing a failure in nucleolar localization and ribosome assembly. Possibly as a consequence of this alteration the proteins are extremely unstable;
b) mutations that affect a later step in ribosome biogenesis. These proteins are able to associate with nucleolar structures but then fail to be assembled into ribosome. In this case the half-life of the proteins, although shorter than WT RPS19, may be longer than the mutated RPS19 of the first class.



Angelini M., Cannata S., Mercaldo V., Gibello L., Santoro C., Dianzani I. and Loreni F. 2007. Missense mutations associated with Diamond-Blackfan anemia affect the assembly of ribosomal protein S19 into the ribosome. Hum Mol Genet 16, 1720-1727.

Chiocchetti A., Gibello L., Carando A., Aspesi A., Secco P., Garelli E., Loreni F., Angelini M., Biava A., Dahl N. et al. 2005. Interactions between RPS19, mutated in Diamond-Blackfan anemia, and the PIM-1 oncoprotein. Haematologica 90, 1453-1462.

Orru S., Aspesi A., Armiraglio M., Caterino M., Loreni F., Ruoppolo M., Santoro C. and Dianzani I. 2007. Analysis of the ribosomal protein S19 interactome. Mol Cell Proteomics 6, 382-393.

GROUP LEADER Claudia Bagni ■ **POSTDOC** Francesca Zalfa ■ **PHD STUDENTS** Valentina Mercaldo • Ilaria Napoli • Boris Eleuteri • Caroline Lacoux ■ **TECHNICAL ASSISTANT** Marcello Giorgi

Identifying key molecules involved in the Fragile X mental retardation syndrome

Zalfa F., Eleuteri B., Dickson K.S., Mercaldo V., De Rubeis S., Di Penta A., Tabolacci E., Chiurazzi P., Neri G., Grant S.G., Bagni C. A new function for the fragile X mental retardation protein in regulation of PSD-95 mRNA stability. Nat Neurosci. 2007 May;10(5):578-87.

Zalfa F., Achsel T., Bagni C. mRNPs, polysomes or granules: FMRP in neuronal protein synthesis. Curr Opin Neurobiol. 2006 Jun;16(3):265-9.

Restivo L., Ferrari F., Passino E., Sgobio C., Bock J., Oostra B.A., Bagni C., Ammassari-Teule M. Enriched environment promotes behavioral and morphological recovery in a mouse model for the fragile X syndrome. Proc Natl Acad Sci U S A. 2005 Aug 9;102(32):11557-62.

Zalfa F., Adinolfi S., Napoli I., Kühn-Hölsken E., Urlaub H., Achsel T., Pastore A., Bagni C. Fragile X mental retardation protein (FMRP) binds specifically to the brain cytoplasmic RNAs BC1/BC200 via a novel RNA-binding motif. J Biol Chem. 2005 Sep 30;280(39):33403-10.

Bagni C., Greenough W.T. From mRNP trafficking to spine dysmorphogenesis: the roots of fragile X syndrome. Nat Rev Neurosci. 2005 May;6(5):376-87.

Zalfa F., Bagni C. Another view of the role of FMRP in translational regulation. Cell Mol Life Sci. 2005 Jan;62(2):251-2.

mRNA localization and regulated translation play central roles in neurite outgrowth and synaptic plasticity. A key molecule in these processes is the Fragile X mental retardation protein, FMRP, which is involved in the metabolism of neuronal mRNAs. Absence or mutation of FMRP leads to spine dysmorphogenesis and impairs synaptic plasticity. Studies that have mainly been performed on the mouse and Drosophila models for Fragile X Syndrome showed that FMRP is involved in translational regulation at synapses, but even 15 years after discovery of the FMR1 gene, the precise working mechanisms remain elusive.

We recently reported an alternative cytoplasmic regulatory function for FMRP: control of mRNA stability. In mice, we found that FMRP binds, in vivo, the mRNA encoding PSD-95, a key molecule that regulates neuronal synaptic signaling and learning. This interaction occurs through the 3' untranslated region of the PSD-95 (also known as Dlg4) mRNA, increasing message stability. Moreover, stabilization is further increased by mGluR activation. Although we also found that the PSD-95 mRNA is synaptically localized in vivo, localization occurs independently of FMRP. Through our functional analysis of this FMRP target we provide evidence that dysregulation of mRNA stability may contribute to the cognitive impairments in individuals with FXS.

A further line of research aims at identifying novel alternative roles for FMRP on translation initiation. Preliminary results indicate that other co-factors may play a role in this scenario.

GROUP LEADERS Luisa Castagnoli • Gianni Cesareni ■ **STAFF SCIENTIST** Stefania Gonfloni ■ **POST-DOCS** Elena Santonico • Michele Tinti ■ **PHD STUDENTS** Roberto Sacco • Emanuela Ferrari • Martina Carducci • Salvatore Corallino ■ **TECHNICAL ASSISTANT** Serena Paoluzi

Characterization of the human domain interaction network

The focus of this project is the characterization of the recognition specificity of families of small domains binding to short extended peptides. Domains binding to peptides that contain a phosphorylated residue or that are rich in prolines mediate a large number of dynamic interactions underlying cell regulatory mechanisms. Over the past few years we have developed and exploited a technology based on the synthesis of thousands of peptides arrayed at high density on a glass chip. The peptide arrays, representing most of the relevant human proteome, are then challenged with the different members of domain families such as 14-3-3, SH2, SH3, WW, EVH, GYF. Analysis of the peptide motifs that bind efficiently to each member of the domain families permits to infer the network of in vivo targets underlying cell physiology.

More recently we have been applying this approach to the interactions mediated by peptides phosphorylated in tyrosines. Residues cycling between a phosphorylated and a non-phosphorylated form play a key role in the modulation of signal transduction. To describe the network linking phosphorylated peptides to their binding domains and to the enzymes that control their phosphorylation levels we have characterized the target preference for most SH2 and phosphatase domains.

The results have been used to train domain specific Neural Networks and to draw a global "naïve" phospho-tyrosine specific interaction network that only takes into account the ability to bind phospho-peptides in an in vitro system. Next we have used a context score that combines in a Bayesian approach orthogonal information, namely tissue co-expression, sub-cellular localization, target sequence conservation in evolution, vicinity in the protein interaction network etc., to rank interaction according to the probability of being functionally relevant. The results of these approaches are being validated by in vivo experiments on a variety of biological problems.

Martinelli S., Torreri P., Tinti M., Stella L., Bocchinfuso G., Flex E., Grottesi A., Ceccarini M., Palleschi A., Cesareni G. et al. 2008. Diverse driving forces underlie the invariant occurrence of the T42A, E139D, I282V and T468M SHP2 amino acid substitutions causing Noonan and LEOPARD syndromes. Hum Mol Genet. 17, 2018-2029.

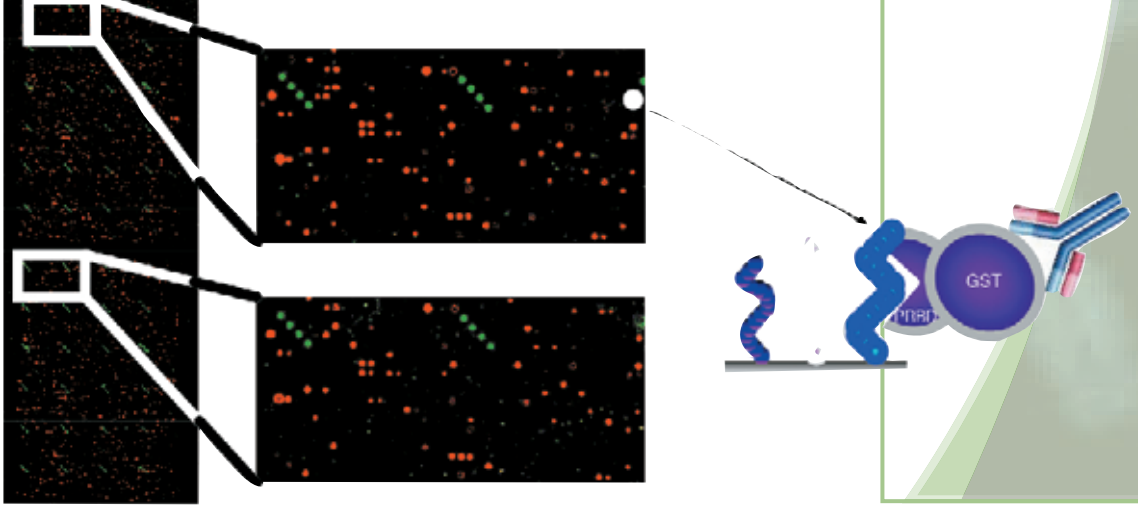
Panni S., Landgraf C., Volkmer-Engert R., Cesareni G. and Castagnoli L. 2008. Role of 14-3-3 proteins in the regulation of neutral trehalase in the yeast Saccharomyces cerevisiae. FEMS Yeast Res 8, 53-63.

Santonico E., Castagnoli L. and Cesareni G. 2005. Methods to reveal domain networks. Drug Discov Today 10, 1111-1117.

Santonico E., Panni S., Falconi M., Castagnoli L. and Cesareni G. 2007. Binding to DPF-motif by the POB1 EH domain is responsible for POB1-Eps15 interaction. BMC Biochem 8, 29.

Cesareni G., Sudol M. and Yaffe M. 2005. Modular protein domains: Wiley-VCH Verlag GmbH & Co. KGaA).

Ceol A., Chatr-aryamontri A., Santonico E., Sacco R., Castagnoli L. and Cesareni G. 2007. DOMINO: a database of domain-peptide interactions. Nucleic Acids Res 35, D557-560.

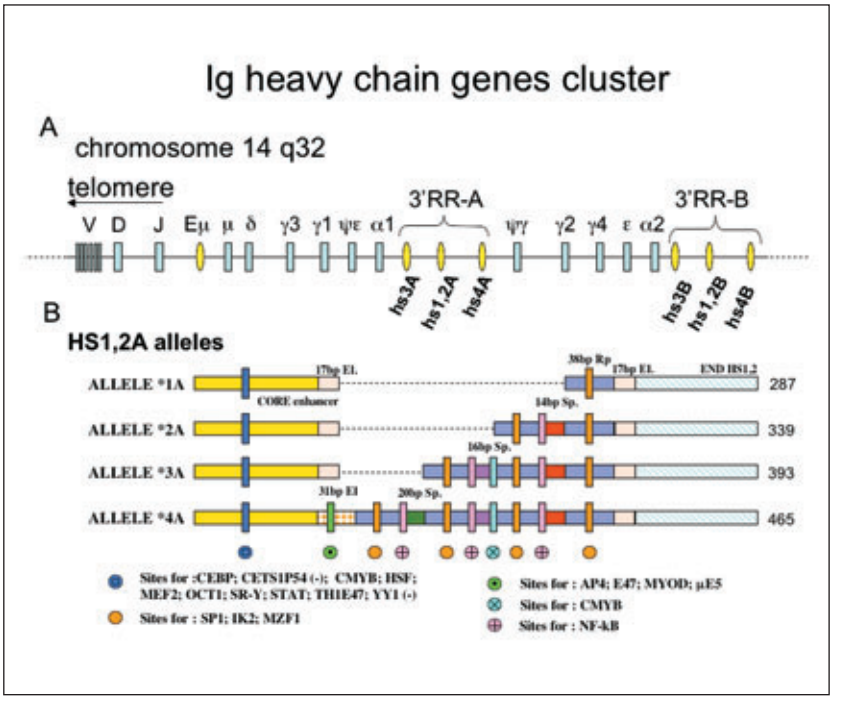


GROUP LEADER Domenico Frezza ■ **STAFF SCIENTISTS** Alberto Fruscalzo • Cristina Martínez-Labarga
■ **PHD STUDENTS** Vincenzo Giambra • Claudia Mattioli • Maria Giufrè ■ **UNDERGRADUATED STUDENT** Sara Tomei
■ **TECHNICAL ASSISTANT** Marco Favaro

Immunoglobulin Heavy chain 3'Regulatory Region polymorphisms associated with normal and abnormal Ig expression

1. Giambra V., Fruscalzo A., Giufre' M., Martínez-Labarga C., Favaro M., Rocchi M., Frezza D. 2005. Evolution of human IgH3'EC duplicated structures: both enhancers HS1, 2 are polymorphic with variation of transcription factor's consensus sites. Gene 346, 105-114.
2. Giambra V., Martínez-Labarga C., Giufre' M., Modiano D., Simpore' J., Gisladottir B.K., Francavilla R., Zhelezova G., Kilic S.S., Crawford M., Biondi G., Rickards O., Frezza D. 2006. Immunoglobulin Enhancer HS1,2 polymorphism: a new powerful anthropogenetic marker. Ann. Hum. Genet. 70, 946-950.
3. Frezza D., Giambra V., Tolusso B., De Santis M., Bosello S., Vettori S., Triolo G., Valentini G., Ferraccioli G. 2007. Polymorphism of immunoglobulin (Ig) enhancer element HS1,2A: allele *2 associates with Systemic Sclerosis. Comparison with HLA-DR and DQ alleles frequency. Ann Rheum Dis. 66, 1210-1215.

The maturation of B lymphocytes proceeds with the maturation of immunoglobulins (Igs). The regulation of these events includes a complexity of interactions far from being understood. The mechanisms leading to the switch of human Ig heavy chain loci are coregulated by the 3'Regulatory Regions (3'RR) located at the 3' of the α-1 and α-2 constant genes. The 3'RRs harbour 3 enhancers and the HS1,2 is central in respect to the other two named HS3 and HS4 (see figure). Moreover, only the HS1,2 enhancer is polymorphic. The polymorphism consists of a satellite sequence repeated from one to four times with different spacers that together modify the pattern of the specific DNA binding sites for complexes of transcription factors. The "*in silico*" analysis predicted a variable number of SP1 and NF-kB sites as confirmed by "*in vitro*" EMSA analysis (1).
In fact allele *2 compared to allele *1 had one extra binding site competed by NF-kB consensus sequence. The difference of structure of the enhancer and the evidence of differential binding to transcription factors of these alleles suggested that the entire process of Ig production could be differently modulated by their presence.
Therefore we investigated any correlation of the HS1,2 alleles with Ig maturation or alteration of Ig production in normal or pathological subjects with immune-diseases.
Our investigation was based on the analysis of the frequency variation of the HS1,2 A alleles in subjects with Systemic Sclerosys, Psoriasis and altered levels of Igs. Indeed the frequency of allele *2 was significantly increased in patients with the immuno-diseases (3). We are still analyzing the haplotypes of the surrounding region of HS1,2 and HS3 to verify if the polymorphisms in subjects with immune-alterations have similar frequencies.



A. Schematic map of the human immunoglobulin heavy chain cluster showing the duplication of four constant genes together with the 3'Regulatory Regions.

B. Schematic representation of the four alleles of the enhancer HS1.2 where the polymorphic region is the 3' part with the variable number of 38bp elements separated by spacers. The elements bear the following consensus for transcription factors: a. conserved core of the enhancer = Oct1; b. = SP1; c. = AP4, E47, mE5; d. = NF-κB; e. = IK2, MZF1; f. = CMYB.

GROUP LEADERS Domenico Frezza • Olga Rickards ■ **STAFF SCIENTIST** Cristina Martínez-Labarga ■ **PHD STUDENTS** Vincenzo Giambra • Claudia Mattioli • Maria Giufrè ■ **TECHNICAL ASSISTANT** Marco Favaro

The HS1,2 polymorphic Ig enhancer as a tool for anthropologic and epidemiologic studies of human populations

The wide number of interactions controlling the maturation process of immunoglobulins and B lymphocytes are far from being understood. However a deeper knowledge of genetic regulatory structures was obtained since the entire genomes of mouse and humans have been unveiled. The heavy chain locus has a duplicated region with four constant "genes" and a large Regulative Region at the 3' of both alpha-1 and alpha-2 genes (3'RR-A and 3'RR-B). Both 3'RRs are considered of primary relevance for the activation of the transcription and switch of the heavy chain region. The 3'RRs of the human immunoglobulins heavy chain harbour three enhancers (HS3, HS1,2 and HS4) that were found to have a synergic activity. These enhancers are conserved from mouse to Apes. The three enhancers are active in both 3'RRs; despite the two enhancers, HS3 and HS4, HS1,2 is polymorphic. One of the possible tools for understanding the interactions of this enhancer with the Ig regulation is the study of their polymorphisms together with the change of function of the entire 3'Regulatory Region. The frequencies of the four alleles of HS1,2-A are highly variable compared to the alleles of HS1,2-B. In fact in the Cameroon and Sardinia populations there was a highly significant difference for the frequencies of HS1,2-A alleles and almost the same frequencies for the HS1,2-B alleles (1). The analysis of eleven populations from the African, Asian and European continents indicates a homogeneity in the Asian populations that is not verified in the European populations where the frequencies of the four alleles have a higher variability. In the Asian population allele *1 is present with the highest frequency (≈ 60%) followed by allele *2 (≈ 30%) and allele *4 (≈ 6%). Allele *3 has the lowest frequency in all the Eurasian area. In the European populations the main variations are observed among allele *1 and allele *2 in a balanced fashion (≈ 40 ± 15%). The African populations compared to the Eurasian resulted to have a very low frequency of allele *2 (≈ 5%) and a high frequency of allele *3 (≈ 25-40%) (2). These variations can have an influence in the immune-response and could have been selected through a gradient of latitude selective factors. The influence of genetic components controlling the humoral immune-response can have a correlation with the morbidity of different populations for infectious disease and auto-immune diseases. When we studied the frequencies of the HS1,2 alleles in the nomad Tuareg population we found that the alleles *2 and *3 have a frequency of 11% and 12% respectively with a mean value between the South-Saharan and Western-Eurasian populations (3). This evidence indicates the relevance of this marker and its possible utility in the anthropologic and epidemiologic studies.

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GROUP LEADER Patrizia Malaspina ■ **PHD STUDENT** Francesca Palmerio ■ **TECHNICAL ASSISTANTS** Paola Blasi
VISITING PROFESSOR JUNE 2006 Matthew J. Picklo, Ph.D.
Dept. of Pharmacology, Physiology and Therapeutics UND School of Medicine, Grand Forks, ND, USA

Functional and molecular variation of SSADH, an enzyme responsible for GABA degradation in humans

Our line of research is aimed at the study of the catabolism of GABA, the major central nervous system inhibitory neurotransmitter. Our interest has evolved from the study at physiological and molecular level of succinic semialdehyde dehydrogenase (SSADH), one of the three enzymes involved in GABA degradation. SSADH complete deficiency results in an autosomal recessive disease called gamma-hydroxybutyric aciduria (4-HBA) for the abnormal accumulation of 4-hydroxybutyrate (GHB) in the brain. GHB possesses a number of unusual neuropharmacological properties. It is used to treat narcolepsy, alcohol and opiate withdrawal, and as a drug of abuse associated to its putative euphoric effects.
We mapped the SSADH gene in a YAC contig covering chromosome 6p22 and characterized its genomic and coding structure. Subsequently, our studies focused on the analysis of SSADH normal and pathological variation. Disease-causing mutations were identified in about fifty 4-HBA families of different geographic origin; *in vitro* expression of missense mutations resulted in a reduction of the activity to less than 5% of the normal control. In recent years, we have characterized new pathological mutations in 4-HBA families (3, 4, 6).
We also identified naturally occurring variants in the general population, some of them reaching polymorphic frequencies and determining a decrease of the enzyme activity as low as 40% of the most common form. This would indicate an inter-individual variation in the endogenous production of GHB and GABA, possibly associated to sub-clinical phenotypes.
A geographical distribution of the coding variants was obtained by genotyping subjects from 60 world-wide populations. This analysis confirmed that c.538C>T polymorphism is the most common: c.538(C) allele shows a wide range of frequencies, with the lowest and highest values in Africa and China, respectively (5). The peculiar pattern of human intra-specific diversity suggested a possible involvement of evolutionary processes that acted on the SSADH gene.
An evaluation of the extent of sequence divergence in terms of nonsynonymous/synonymous substitution rate (*dN*/*dS*) was obtained by comparison with 6 primate sequences. The finding of a three times higher *dN*/*dS* ratio displayed by the human lineage raises the possibility of an acceleration in the rate of nonsynonymous substitutions in the lineage leading to humans.
Inter-specific analyses also made it possible to infer the ancestral state at all the variable positions. In all but one polymorphism, the most common allele found in humans is represented by the ancestral state, which is shared with primates.
By contrast, c.538(C) allele represents the derived allele proceeding to fixation.
The unexpected pattern of intra-specific allele distribution compared to the inter-specific findings outlines the possibility of a positive selection that specifically acted in the human lineage, possibly by virtue of the advantage conferred by the maximal activity associated with c.538 (C) allele (2).

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GROUP LEADER Guido Modiano ■ **STAFF SCIENTIST** Bianca Maria Ciminelli ■ **POST-DOCS** Fiorenza Pompei • Cinzia Ciccacci

Evolution of the CFTR (Cystic Fibrosis conductance Transmembrane Regulator) gene in Europe

Since Cystic Fibrosis (CF) is the most common severe genetic disease in Europe, the CFTR gene is one of the best studied genes both at the epidemiological and the clinical level and more than one thousand alleles have been identified (http://www.genet.sickkids.on.ca/cftr/app). Many alleles are recessive CF-causing alleles.

By contrast, the random variability of this gene remained much less studied until few years ago when the results obtained by examining a random sample of 700-800 Europeans was published (Modiano et al., 2005) this confirming the high degree of variability of the M470V site in Europeans ($H_{Europe} \approx 0.48$).

Haplotype variability of the CFTR gene – More recently we conducted a study at the haplotypic level by comparing the intra-allelic variability of the CFTR-M with that of the CFTR-V allele (Pompei et al., 2006). These haplotypic variabilities were estimated by direct counting on the MM and VV homozygotes. The main result of this comparison is that almost all the CFTR gene variability is restricted to the M allele (the ancestral one).

A possible prospective strategy for preventing Cystic Fibrosis – On the basis of the above mentioned result (CFTR variability confined to the M allele), we have proposed a two-phase counselling prospective strategy (Ciminelli et al., 2007). The first phase should consist of genotyping all the couples for the M470V site with the aim of subdividing them in different classes having different likelihood of being 'an at risk couple' (in the decreasing order: MM x MM; MM x MV; and so on… VV x VV). The second phase should consist of an in depth analysis only of the couples with a risk higher than a suitable threshold.

A selective hypothesis to explain the 'high' CF alleles frequency in Europe – Since the cumulative CF alleles frequency is too high for an ensemble of lethal recessive alleles, a heterozygote's advantage has long been hypothesized. The CFTR protein is strongly involved in water excretion by epithelial cells; thus it has been proposed that the selective factor has been a greater resistance in CF heterozygotes to diarrhea-causing factors such as cholera. We have recently proposed that the main diarreha-causing selective factor is, instead, the milk rich (hence lactose rich) diet adopted by cattle-breeding Europeans when they were still lactose intolerant (Modiano et al., 2007).

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Human evolutionary genetics

Cruciani F., La Fratta R., Trombetta B., Santolamazza P., Sellitto D., Colomb E.B., Dugoujon J.M., Crivellaro F., Benincasa T., Pascone R., Moral P., Watson E., Melegh B., Barbujani G., Fuselli S., Vona G., Zagradisnik B., Assum G., Brdicka R., Kozlov A.I., Efremov G.D., Coppa A., Novelletto A., Scozzari R. 2007. Tracing Past Human Male Movements in Northern/Eastern Africa and Western Eurasia: New Clues from Y-chromosomal Haplogroups E-M78 and J-M12. Mol Biol Evol. 24:1300-1311.

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The Y chromosome is an optimal tool for the reconstruction of the ancestry and worldwide dispersal of human populations. The progressive accumulation of mutations in the male-specific portion (MSY) of the chromosome, without the reshuffling effect of recombination, makes it possible to reconstruct a unique phylogeny. The main and long-term aim of this research group is to contribute to the reconstruction of a populational history of Europe based purely on genetic grounds and thus free of the bias intrinsically present in all reconstructions based on the archaeological record. In fact, such a goal can be reached only with genetic tools, so condensing the contributions of all subjects who inhabited the continent and took part in the continuity of its human settlement. The added value of this research pertains to both advances in genetics (intrinsic value) and in interdisciplinarity (extrinsic value).

Research line: tempo and mode of the formation of the European patrilinear gene pool; inferences on the immigration, range expansion, demographic expansion, resettlement and drift processes in European populations at large.

Research mid-term goals: reconstruction of molecular radiation between and within Y-chromosomal lineages defined by Single Nucleotide Substitution (SNP) and Simple Tandem Repeat (STR) variation. Phylogeographic analyses of haplogroups. Genetic dating of the antiquity of specific molecular types to define upper and lower bounds for their introduction into extant gene pools.

Research methods: Collection of male DNA from subjects living in all areas of Continental Europe and Northern Africa, with special reference to the Mediterranean area. These aspects of the research are attained by a large number of collaborations with medical and anthropology research groups in European and non-European countries.

Typing of SNP known to identify lineages relevant to European history and pre-history. Search for additional SNP variation by means of specifically designed re-sequencing programs. Optimization of search strategies.

Typing for STR variation.

Data-analysis by partition of molecular variance. Spatial analyses. TMRCA and population parameter estimation by coalescent methods. Development of *ad hoc* methods.

The human evolutionary genetics laboratory is equipped with all the basic instruments for molecular biology needed to carry out the work described above (PCR Thermal Cyclers, electrophoresis apparatuses). It includes 6 benches that can host up to 12 working persons at the same time. Automated DNA analyses for both SNPs and STRs make use of an ABI3100avant DNA sequencer, shared with other groups.

Fund raising is through submission to national or international agencies of specific projects, mostly in collaboration with other research groups.

Dissemination is through papers in scientific journals and contribution to two initiatives for the non-specialized audience:

the University of Calabria OPENLAB (http://biologia.unical.it/openlab) and the University "Tor Vergata" Master in Science and Technology Dissemination (http://comunicazione-scienza.uniroma2.it/).

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Evolution of karyotype rearrangements: i) evolutionary cytogenetics; ii) environmental mutagenesis

Evolutionary cytogenetics. The subject of this research field is the expansion and accumulation of several underdominant chromosomal rearrangements for the evaluation of their eventual role in speciation.
Metaphases of spermatocytes II were studied in mice with a reconstructed karyotype, heterozygous for several centric fusions, (1-4) by means of Fluorescent In Situ Hybridization (FISH) techniques. Using telomeric DNA probes, it was demonstrated that chromosomes with the same shape tend to co-segregate during first meiotic division (metacentrics with metacentrics and acrocentrics with acrocentrics), suggesting a chladistic role for such rearrangements.
Using whole-chromosome-specific painting probes non-disjunction rates of specific chromosomes (1, 4, 6 and 14) were evaluated and no epistatic interaction among trivalents on non-disjunction rates was demonstrated to take place. We also studied the possible influence of either genetic or karyotypic background in affecting cosegregation, nondisjunction rates and epistatic interactions in mice with a reconstructed karyotype, heterozygous for several centric fusions. We found that such factors do not influence the proneness to nondisjunction of specific chromosomes.
The same phenomena will be studied in mice caught in a hybrid zone between two chromosomal races, one normal (2n = 40 acrocentric chromosomes) and one homozygous for 9 centric fusions (2n = 22, chromosomes, 18 metacentrics and 4 acrocentrics).
Environmental mutagenesis. This research field is focused on the detection of mutagenic pollution of natural waters using cytogenetic tests (micronucleus test) performed in tissue samples from suitable organisms as bioindicators, either plant or animal species, according to the specific matter under investigation.
Micronucleus test in circulating erythrocytes of *Cyprinus carpio* and in root tips of *Vicia faba* have been used to test the clastogenic/aneugenic activity of by-products produced by the disinfection process for surface fresh-water potabilization. Experiments were carried out in a pilot potabilization-plant present in Comune di Castiglione del Lago (PG), supplied with surface water from Lago Trasimeno. These lake-waters were shown to contain very high concentrations of total organic carbon (TOC) and bromides, suitable to form mutagenic by-products, from interacting with different kinds of disinfectants, namely NaClO, ClO_2 e CH_3-COOOH. Since positive results were found in both plant and fish organism exposures, particularly observed after chlorinate compound water treatments, the same test had also been used to evaluate the formation of genotoxic by-products following the exposure of fish and plants to mixtures of disinfectants and commercial humic acids, confirming the production of mutagenic by-products from chlorinate disinfectants employment in humic-acid rich natural waters. Moreover, a correlation between oxidative stress and genetic damage induction was found, with the possibility for these compounds to generate organochlorine by-products, also able to perturb CYP-mediated reactions. The potential mutagenic effect of water samples collected in different points of the drinkable water nets in different Italian towns is also studied.

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GROUP LEADERS Luciano Paolozzi • Patrizia Ghelardini ■ **STAFF SCIENTIST** Gustavo Di Lallo ■ **POST-DOCS** Marta Fagioli • Valeria D'Ulisse ■ **PHD STUDENT** Lucia Grenga

Interaction web, biological role and phylogenetic conservation of proteins forming the Prokaryotic "minimal commune divisome"

D'Ulisse V., Fagioli M., Ghelardini P. and Paolozzi L. 2007. Three functional subdomains of the Escherichia coli FtsQ protein are involved in its interaction with the other division proteins. Microbiology. 153,124-38.

Fadda D., Santona A., D'Ulisse V., Ghelardini P., Ennas M.G., Walen M.B. and Massida O. 2007. Streptococcus pneumoniae DivIVA: localization and interactions in a MinCD-free context. J Bacteriol. 189,1288-98.

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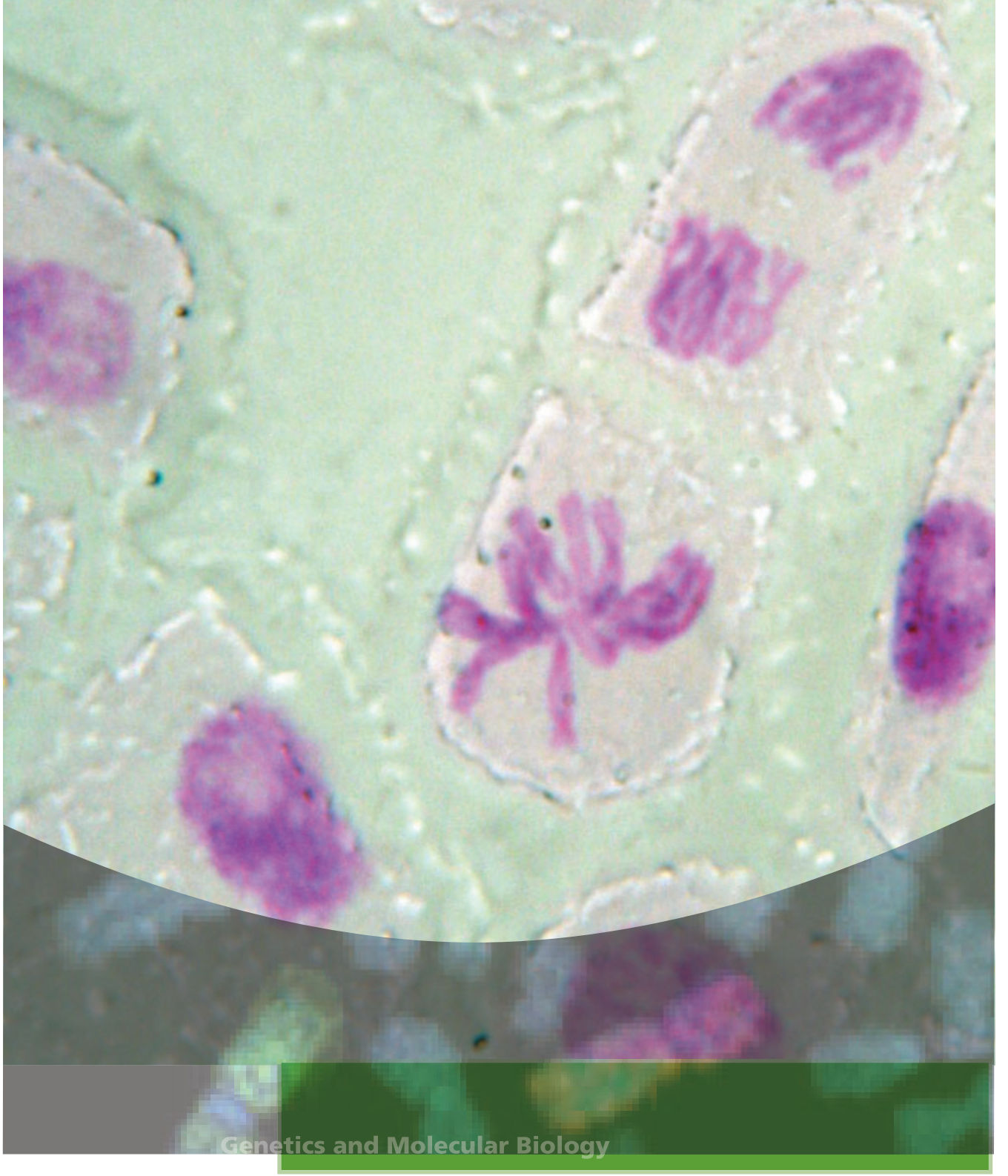
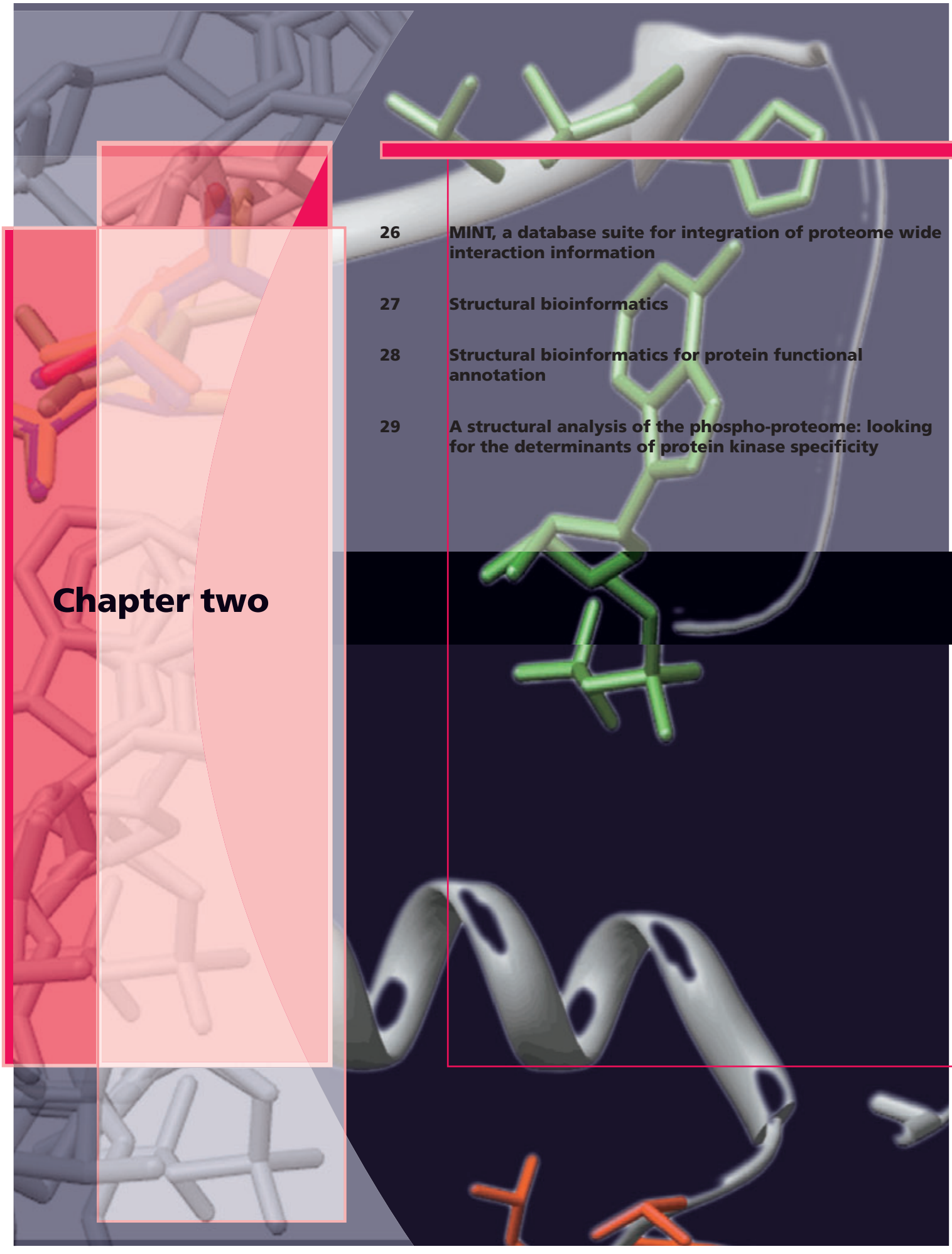
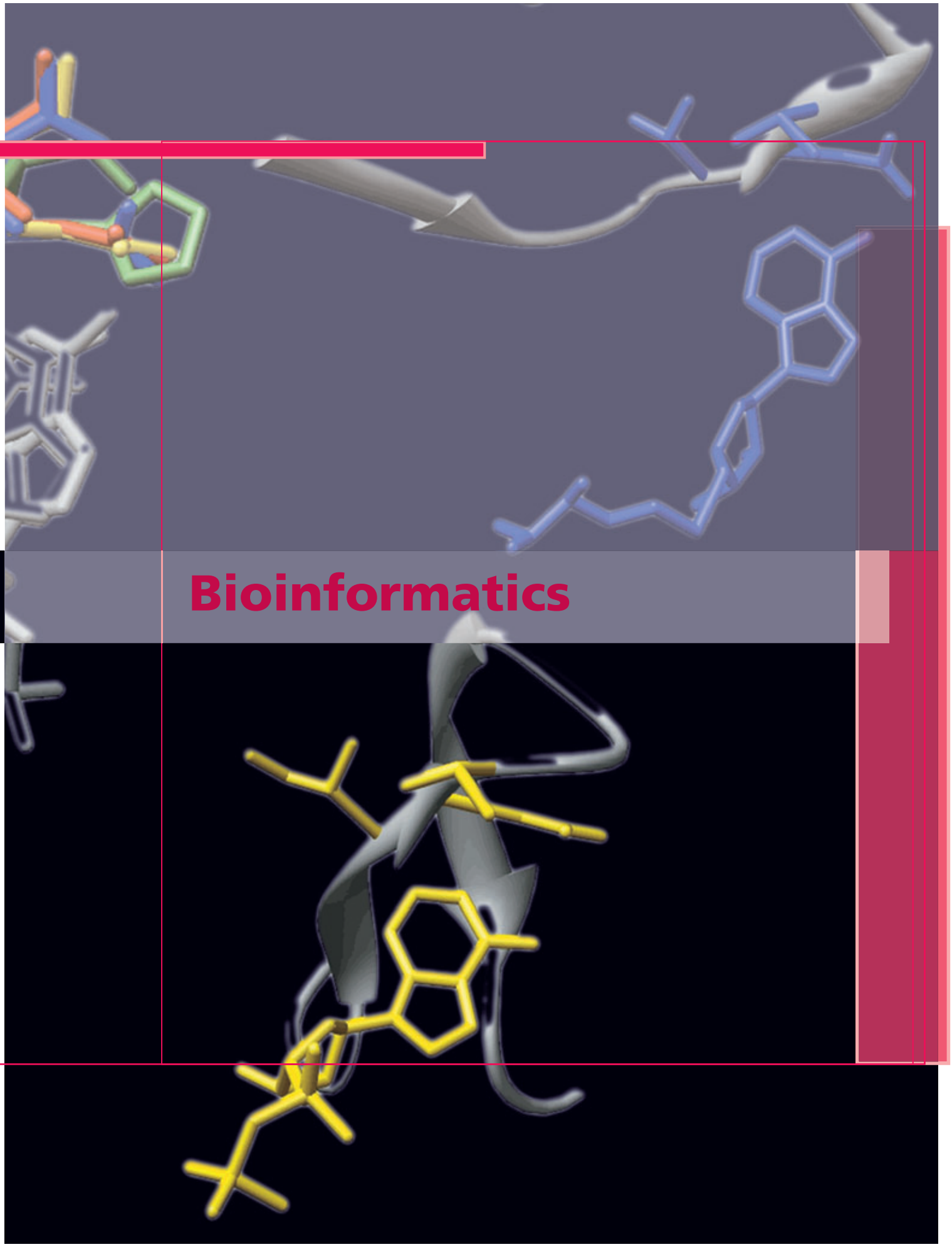
Bacterial cell division is an essential process, whose mechanism is still only partially understood. Interest in this process is due to both an intrinsic biological curiosity and to the possibility to exploit the cell division proteins as primary targets for novel broad-spectrum antibacterial drugs. A key step in the process is the dynamic assembly of the division machinery, called the septosome or divisome.
This structure, that forms at a precise moment of the cell cycle, requires the participation of at least twelve proteins, called Fts, that are targeted to the mid-cell precisely for the rod shaped bacteria, following a hierarchic and interdependent order. Studies of colocalization of the Fts proteins fused with the GFP allowed to reconstruct their sequence of recruitment at the division site. During this process, FtsZ monomers polymerize to form a ring, the Z-ring, which constitutes the scaffold for the other cell division proteins and the cytokinesis machinery. In Prokaryotes, in the divisome formation there participate, along with generally conserved Fts proteins, a series of proteins specific for each species. Among the conserved proteins, three that share a similar structure are particularly interesting: FtsQ, FtsI and FtsL. FtsI, involved in septal peptidoglycan biosynthesis, is a target for penicillin. The fact that many mutated forms of this protein become resistant to this class of antibiotics is at the basis of the medical interest of its study. The way of how these proteins assembly at the division start or their disassembly at the end of the process is still unknown. Analogously, the signal(s) that cause the assembly and disassembly of the structure and its targets remain(s) to be elucidated. Several groups studied the protein-protein interaction (PPI) among the various septosome components. Our group recently described the whole *E. coli* division protein PPI web as well as that of *S. pneumoniae*. Our results showed that the PPI web is extremely complex: generally, each protein undergoes to multiple interactions with both itself and other bacterial partners also forming multimeric complexes. Comparison of *E. coli* and *S. pneumoniae* division interactomes showed the existence of a high conservation that allows the proteins of an organism to interact with the corresponding orthologs of the other, in spite of the phylogenic distance between these two microorganisms. Analogously, we observed complementation between pairs of homologous proteins of *S. pneumoniae* and *E. coli*. Taken as a whole, these data suggest the existence of a prokaryotic "minimal commune divisome", i.e. a common cytokinesis apparatus that differentiates in various species depending on additional activities.
This hypothesis could make it possible to reveal both a unitary mechanism in the division process and the identification of the characteristics aspects of each species.



Genetics and Molecular Biology



Chapter two



Bioinformatics

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MINT, a database suite for integration of proteome wide interaction information

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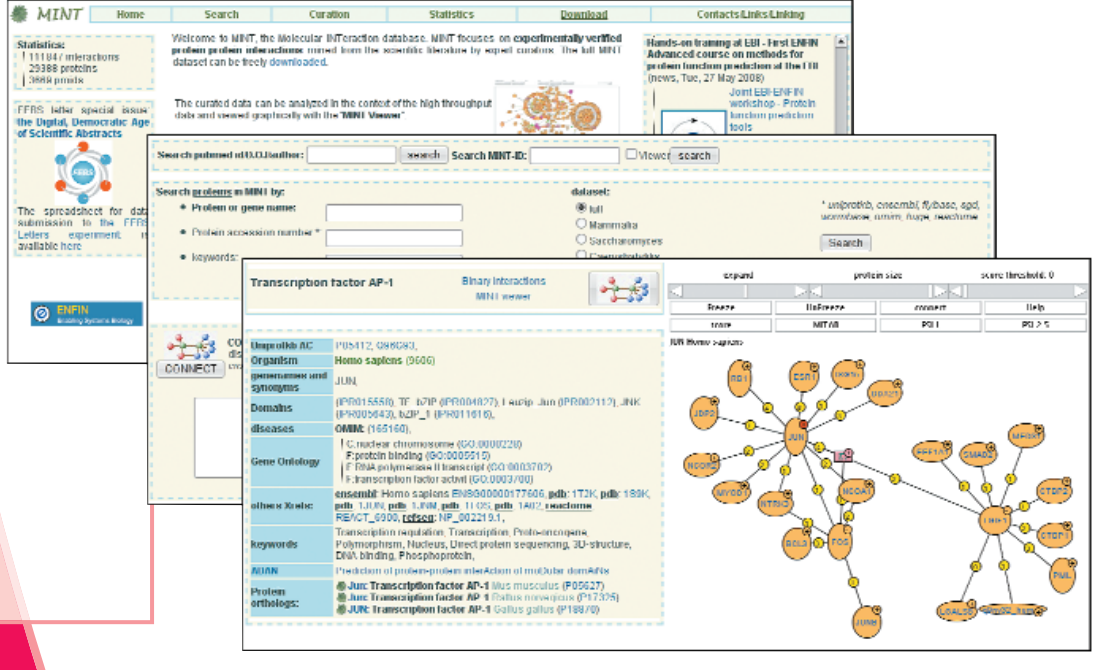
Persico M., Ceol A., Gavrila C., Hoffmann R., Florio A. and Cesareni G. 2005. HomoMINT: an inferred human network based on orthology mapping of protein interactions discovered in model organisms. BMC Bioinformatics 6 Suppl 4, S21.

The corpus of scientific literature has reached a size that useful data are now hard to retrieve. For instance many articles in the biological field describe relationships between entities (gene, proteins, small molecules...). Yet this crucial information cannot be efficiently used because of the difficulties in retrieving it automatically as unstructured text dispersed throughout millions of different articles.
After recognizing this problem our group started in 2001 to develop MINT, a protein interaction database, and has endeavored to populate it with data extracted by expert curators from published literature. Over the past years MINT has grown to become one the most accessed protein interaction databases. Together with DIP in California and INTACT at the European Bioinformatic Institute MINT is part of the iMEX consortium with the goal of distributing curation work, avoiding effort overlap and sharing curated data.
More recently a number of specialized databases have been added to the MINT website to store data about domain interactions (DOMINO), human interactions as deduced from experiments in model organisms (HomoMINT) or protein localization (CellMINT). All these databases can be freely accessed and data downloaded from the MINT homepage (http://mint.bio.uniroma2.it/mint).



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Structural Bioinformatics

Knowledge of the structure and function of the relevant macromolecules, revealed by X-ray and NMR analysis, is central to the interpretation and exploitation of the experimental information. The application of computer technology to biomolecules, the so-called "Structural Bioinformatics" based on the 3D structures of macromolecules, is today an important part of biotechnology and is a useful instrument to guide and design experiments. By using comparative modelling, electrostatic analysis and classical molecular dynamics simulations (MD) we study the structure-dynamics-function relationship of biological macromolecules. In the simulation studies we also compare wild-type enzymes with specific mutants to explain observed experimental differences and to predict bio-molecular properties to be used in conjunction with advanced experimental techniques.

Some examples of studies carried out in our laboratory are summarized here.

The equilibrium properties of a mutant dimeric *Photobacterium leiognathi* Cu,Zn superoxide dismutase has been studied, experimentally and computationally, and compared with the native enzyme. Experimental pressure-dependent dissociation is observed for the mutant monitoring the tryptophan fluorescence shift.

The simulative approach permits us to define a path for the dissociation of the dimer and to calculate the effective force involved in the process. The calculated free energy difference is close to the experimental one indicating that the theoretical reaction scheme is able to reproduce the process (Maragliano *et al.*, 2005).

The p63 protein is crucial for epidermal development. Its mutations, G534V and T537P, cause the human genetic disease ankyloblepharonectodermal dysplasia-clefting syndrome (AEC). p63 and its mutants have been studied by MD and the analysis of the structural dynamic properties of the mutants, in comparison with the wild type, have permitted us to detect the molecular causes for this pathology (Cicero *et al.,* 2006).

Dimeric lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is the target receptor for oxidized low density lipoprotein (OxLDL) in endothelial cells and plays a crucial role in the atherosclerosis plaque formation. MD simulations of the wild-type LOX-1 and of the Trp150Ala mutant C-type lectin-like domains have been carried out to gain insight into the severe inactivation due to this mutation. This study has indicated that the molecular mechanism of OxLDL-LOX-1 recognition is mainly electrostatic providing the route for the development of therapeutical OxLDL antagonists (Falconi *et al.*, 2007a).

The structural dynamics of the DNA binding domains of the human papillomavirus strain 16 and the bovine papillomavirus strain 1, alone and complexed with their DNA targets, have been investigated by MD simulations and NMR analysis (Falconi et al., 2007b and 2008). The simulations underline different dynamical features of the protein scaffolds and a different mechanical interaction of the two proteins with DNA, showing that the two transcription factors utilize a different strategy in DNA recognition and deformation.

Maragliano L., Falconi M., Sergi A., Cioni P., Castelli S., Lania A., Stroppolo M.E., Strambini G., Ferrario M. and Desideri A. 2005. Experimental and simulative dissociation of dimeric Cu,Zn superoxide dismutase doubly mutated at the intersubunit surface. Biophys J. 88, 2875-2882.

Cicero D.O., Falconi M., Candi E., Mele S., Cadot B., Di Venere A., Rufini S., Melino G. and Desideri A. 2006. NMR structure of the p63 SAM domain and dynamical properties of G534V and T537P pathological mutants, identified in the AEC syndrome. Cell. Biochem. Biophys. 44, 475-489.

Falconi M., Biocca S., Novelli G. and Desideri A. 2007a. Molecular dynamics simulation of human LOX-1 provides an explanation for the lack of OxLDL binding to the Trp150Ala mutant. BMC Struct Biol. 7, 73-83.

Falconi M., Santolamazza A., Eliseo T., De Prat-Gay G., Cicero D.O. and Desideri A. 2007b. Molecular dynamics of the DNA-binding domain of the papillomavirus E2 transcriptional regulator uncover differential properties for DNA target accommodation. FEBS J. 274, 2385-2395.

Falconi M., Oteri F., Eliseo T., Cicero D.O. and Desideri A. 2008. MD Simulations of Papillomavirus DNA-E2 Protein Complexes Hints at a Protein Structural Code for DNA Deformation. Biophysical Journal. In the press.

GROUP LEADER Manuela Helmer-Citterich ■ **POST-DOC** Gabriele Ausiello ■ **PHD STUDENT** Pier Federico Gherardini

Structural bioinformatics for protein functional annotation

Ausiello G., Via A., Helmer-Citterich M. 2005a. Query3d: a new method for high-throughput analysis of functional residues in protein structures. BMC Bioinformatics, 6 (Suppl 4):S5.

Ausiello G., Zanzoni A., Peluso D., Via A., Helmer-Citterich M. 2005. pdbFun: Mass selection and fast comparison of annotated PDB residues. Nucl.Acids Res., 33, 133-137.

Ausiello G., Peluso D., Via A., Helmer-Citterich M. 2007. Local comparison of protein structures highlights cases of convergent evolution in analogous functional sites. BMC Bioinformatics, 8 (Suppl.1): S24.

Ferrè F., Ausiello G., Zanzoni A., Helmer-Citterich M. 2005. Functional annotation by identification of local surface similarities: a novel tool for structural genomics. BMC Bioinformatics. 6, 194.

Gherardini P.F., Wass M.N., Helmer-Citterich M., Sternberg M.E. 2007. Convergent evolution of enzyme active sites is not a rare phenomenon. J. Mol. Biol., 372, 817-845.

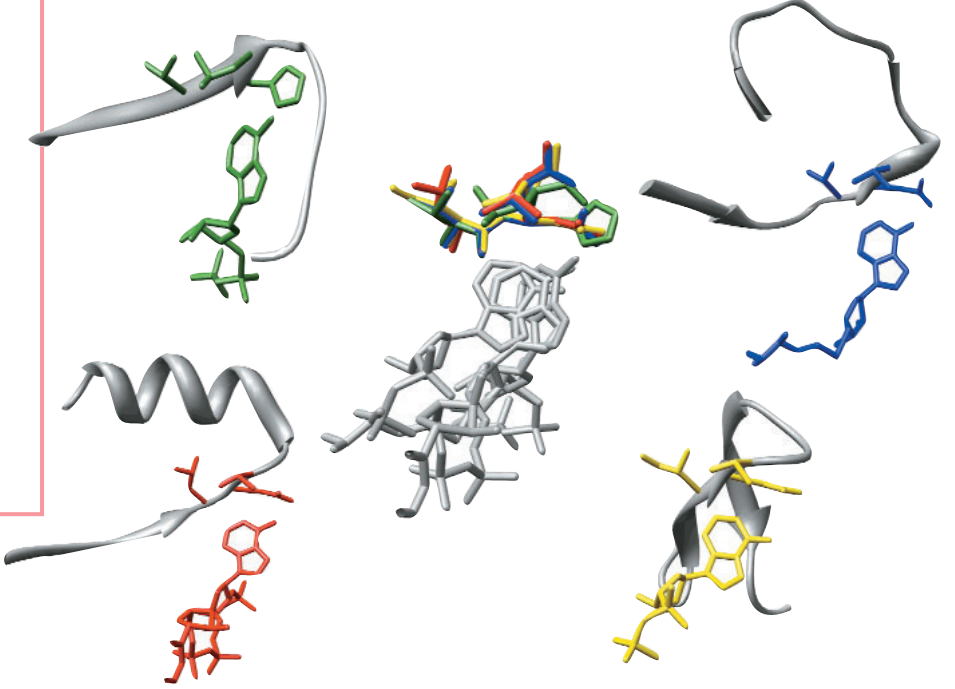
The ever increasing number of protein structures determined by structural genomic projects has spurred much interest in the development of methods for structure-based function prediction. Such methods usually follow a comparative approach, assigning function *by similarity*, or rely on the analysis of the physico-chemical features of the protein surface.

We chose a comparative approach and developed the Query3d method for the identification of local structure similarities (Ausiello *et al.,* 2005a). This method has also been made available as the innovative pdbFun webserver (Ausiello *et al.,* 2005b). pdbFun integrates residue level functional annotations with the Query3d algorithm, so that the residues to be used in a comparison run can be selected on the basis of functional information.

This method can be used for associating a molecular function to proteins whose structure was derived in Structural Genomic projects (Ferrè *et al.,* 2005), or to propose new functions for proteins already characterized, such as the ability to bind specific ligands or to perform a given catalytic activity. Following this line of research, we are also interested in the application of local comparison methods to the study of molecular evolution. We have indeed applied Query3d to the discovery of hidden evolutionary relationships between proteins and to the identification of significant cases of convergent evolution (Ausiello *et al.,* 2007; Gherardini *et al.,* 2007).

Future developments include the analysis of protein-ligand binding sites, in search for the molecular determinants of the specificity of interaction between small 3D motifs (2-3 residues) and definite ligand fragments even in the context of different molecules.

All information on the group research projects is available on the website of the Centre for Molecular Bioinformatics (http://bioinformatica.uniroma2.it/).



GROUP LEADER Manuela Helmer-Citterich ■ **POST-DOC** Allegra Via ■ **PHD STUDENTS** Enrico Ferraro • Tecla Lucca • Andreas Zanzoni

A structural analysis of the phospho-proteome: looking for the determinants of protein kinase specificity

The phosphorylation of specific protein residues is a crucial event in the regulation of several cellular and pathogenic processes, acting on activation, deactivation or recognition of the target protein. Unraveling the rules of kinase specificity is of crucial importance for discriminating true phosphorylating sites (P-sites) among the huge amount of potential sites. To this aim, we did pursued two different approaches: the development of computational methods for the inference of the specificity of interaction of protein domains involved in the regulation of phosphorylation (Ferraro *et al.,* 2005; Ferraro *et al.,* 2006; Ferraro *et al.,* 2008) and the analysis of all experimentally verified phosphorylation sites (Zanzoni *et al.,* 2007). In the latter case, we collected all available structural information on P-sites (accessibility to the solvent, secondary structure, H-bonds, etc.) and on the 3D region around them and performed a comparison with a negative control, in order to detect statistically significant signals that can help identify characteristics that are P-site-specific. An informative selection of the structural features analysed will be used to develop a predictor for the identification of the protein kinase able to phosphorylate a specific protein and to suggest the possible substrates of a kinase or kinase family.

The group also develops web servers for making our methods available to the scientific community (Via *et al.,* 2005; Via *et al.,* 2007).

All information on the group research projects is available on the website of the Centre for Molecular Bioinformatics (http://bioinformatica.uniroma2.it/).

Ferraro E., Via A., Ausiello G., Helmer-Citterich M. 2005. A neural strategy for the inference of SH3 domain-peptide interactionspecificity. BMC Bioinformatics, 6 Suppl 4, S13.

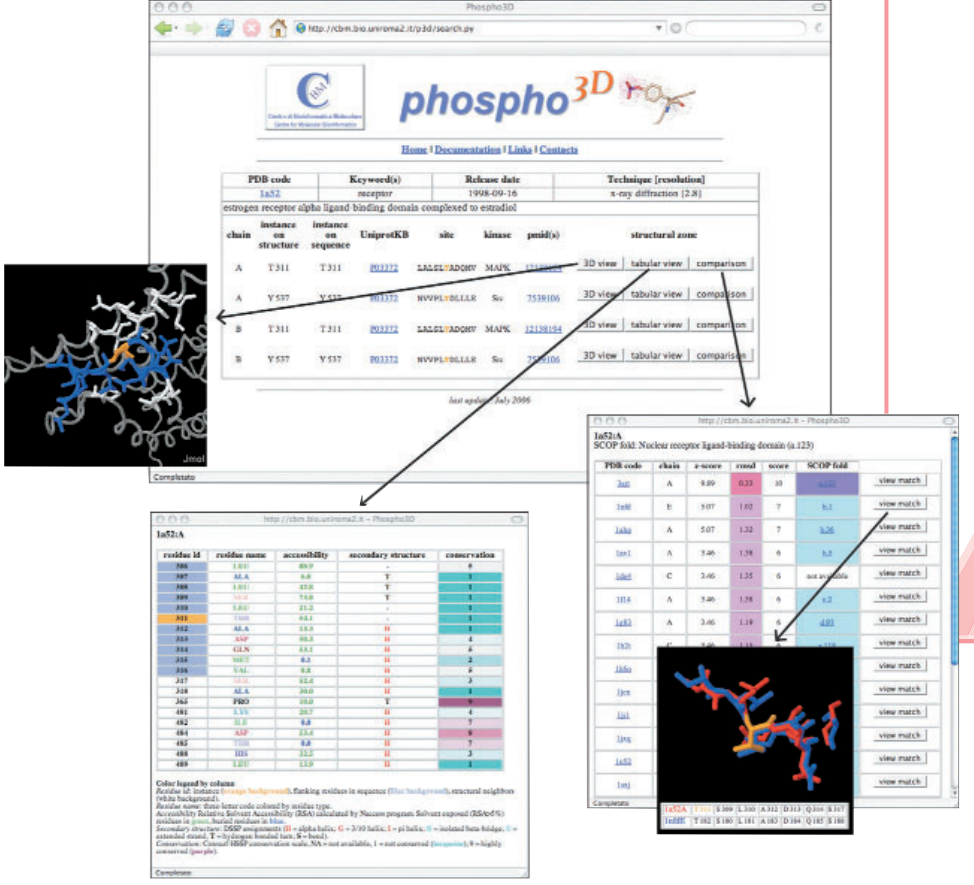
Ferraro E., Via A., Ausiello G., Helmer-Citterich M. 2006. A novel structure-based encoding for machine-learning applied to the inference of SH3 domain specificity. Bioinformatics, 22, 2333-2339.

Ferraro E., Peluso D., Via A., Ausiello G., Helmer-Citterich M. 2007. SH3-Hunter: discovery of SH3 domain interaction sites in proteins. Nucleic Acid Res. 35 (Web Server issue):W451-454.

Via A., Peluso D., Gherardini P.F., De Rinaldis E., Colombo T., Ausiello G., Helmer-Citterich M. 2007. 3dLOGO: a web server for the identification, analysis and use of conserved protein substructures. Nucleic Acid Res. 35(Web Server issue):W416-419.

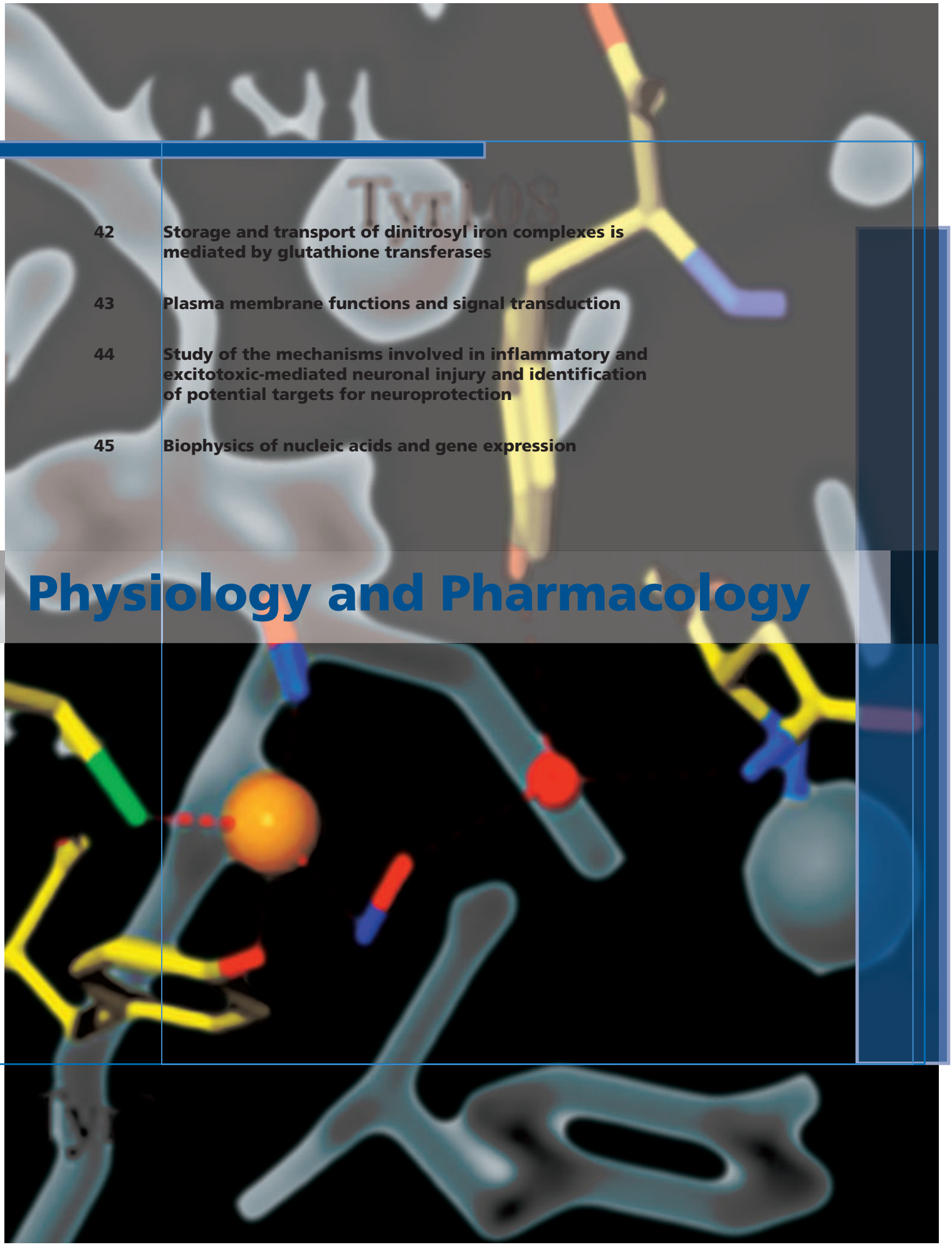
Via A., Zanzoni A., Helmer-Citterich M. 2005. Seq2Struct: aresource for establishing sequence-structure links. Bioinformatics. 21, 551-553.

Zanzoni A., Ausiello G., Via A., Gherardini P.F., Helmer-Citterich M. 2007. Phospho3D: a database of three-dimensional structures of protein phosphorylation sites. Nucleic Acids Res., 35 (Database issue):D229-231.



Chapter three

Biochemistry,



Physiology and Pharmacology

GROUP LEADER Andrea Battistoni ■ **POST-DOCS** Serena Ammendola • Melania D'Orazio • Francesca Pacello ■ **PHD STUDENT** Patrizia Petrarca

Transition metals and metalloproteins in the host-pathogen interaction

1. Berlutti F., Morea C., Battistoni A., Sarli S., Cipriani P., Superti F., Ammendolia M.G. and Valenti P. 2005. Iron availability influences aggregation, biofilm, adhesion and invasion of Pseudomonas aeruginosa and Burkholderia cenocepacia. Int. J. Immunopath. Pharmacol. 18, 661-670.
2. Ammendola S., Ajello M., Pasquali P., Kroll J.S., Langford P.R., Rotilio G., Valenti P. and Battistoni A. 2005. Differential contribution of sodC1 and sodC2 to intracellular survival and pathogenicity of Salmonella enterica serovar Choleraesuis. Microbes infect. 7, 698-707.
3. D'Angelo P., Pacello F, Mancini G., Proux O., Hazemann J.L., Desideri A. and Battistoni A. 2005. X-ray absorption investigation of a unique protein domain able to bind both Cu(I) and Cu(II) at adjacent sites of the N-terminus of Haemophilus ducreyi Cu,Zn superoxide dismutase. Biochemistry. 44, 13144-13150.
4. De Domenico I., Lania A., Bonaccorsi di Patti M.C., Battistoni A, Musci G., Desideri A. 2006. Purification and characterization of recombinant Caulobacter crescentus Cu,Zn superoxide dismutase. Biochim.Biophys. Acta – Proteins and Proteomics. 1764, 105-109.
5. Ammendola S., Pasquali P., Pistoia C., Petrucci P., Petrarca P., Rotilio G. and Battistoni A. 2007. The high affinity Zn2+ uptake system ZnuABC is required for bacterial zinc homeostasis in intracellular environments and contributes to virulence of Salmonella enterica. Infect. Immun. 75, 5867-5876.
6. Ammendola S., Battistoni A., Pasquali P. Salmonella enterica strains with reduced pathogenicity, method for their preparation and uses therof. International patent. Application No: PCT/IT2007/000410 - Pub. No: WO/2007/148363.

Transition metals are essential cofactors in a large number of proteins where they play catalytic and/or structural roles. Therefore, all organisms have developed mechanisms to obtain adequate amounts of metals such as iron, zinc, manganese and copper, while avoiding unnecessary and potentially toxic intracellular metal accumulations. The problem of adequate metal recruitment is extremely acute for bacterial pathogens, as they colonize environments where metals are scarcely available in accessible forms. In fact, within the host cells metals are sequestered in forms which limit their availability for invasive microorganisms. In this framework, our research focuses on different aspects of transition metals in the host-microbe interactive biology.

We have shown that iron availability modulates biofilm formation and invasion of epithelial cells by *Pseudomonas aeruginosa* and *Burkholderia cenocepacia*, two opportunistic pathogens responsible of lung infections in Cystic Fibrosis (CF) (1). As high iron concentration characterizes the airway surface liquid of CF patients, we are currently investigating the possibility of combatting chronic infections in the CF lung through strategies aimed at restoring normal metal homeostasis.

Several enzymes facilitating bacterial survival within the infected host contain transition metals. This class of proteins includes periplasmic Cu,Zn superoxide dismutase (Cu,ZnSOD), coded in bacteria by *sodC* genes, which can shield bacteria from the reactive oxygen species actively produced by inflammatory cells.

We are investigating the regulation and role of *sodC* genes in pathogens (2) and the peculiar structural/functional properties of Cu,ZnSODs from a variety of prokaryotic sources (3, 4). For example, we have shown that the Cu,ZnSODs from a few pathogens possess divalent metal binding N-terminal extensions, which favour the uptake of the enzyme's prosthetic metals in environments where their concentration is low (3).

To investigate the relevance of zinc in the host-pathogen interaction we have constructed *Salmonella enterica* strains lacking the ZnuABC high affinity Zn^{2+} transporter (5). Such mutants grow normally in rich media, but display little ability to multiply in media deprived of zinc and a dramatically reduced pathogenicity in mice. In agreement, *znuABC* is expressed only in bacteria grown in environments poor in zinc or in intracellular salmonellae recovered either from cultured cells or from the spleens of infected mice. These studies show that the free metal quota available for bacterial growth in the infected animal is limited, despite its apparent elevated concentration within cells and in plasma, and reveal an unpredicted parallelism between the mechanisms of iron and zinc sequestration in the host-pathogen relationships.

We have also demonstrated that *S. enterica znuABC* mutant strains prime a cell-mediated immune response, which confers a solid and durable immune-based protection against challenge infections with virulent strains. These findings suggest the possibility of using *znuABC* mutant strains for the production of novel anti-*Salmonella* vaccines (6).

Effects of different garlic extracts on the cell cycle and the viability of HepG2 hepatoma cells

Garlic extracts, either aqueous or oily, are commonly employed to prepare garlic derivative supplements used as nutraceuticals for the treatment of different pathologies. In this study, we investigated the effects of water garlic extracts from two different areas of Italy well known for garlic production, Latina (GEL) and Sulmona (GES), on cell cycle and death of HepG2 hepatoma cells. The effects of the treatments with GEL and GES were also compared with the oil-soluble sulfur compound of garlic, diallyl disulfide (DADS). GEL and GES induced a p53/p21-dependent cell cycle arrest in G2/M phase and apoptosis, although to a different extent, whereas DADS, under the experimental conditions used, was not detrimental to HepG2 cells. GEL and GES committed HepG2 cells to apoptosis by the activation of c- Jun-NH2 terminal kinase (JNK)/c-Jun phosphorylative cascade without a detectable increase in the flux of reactive oxygen species.
Moreover, differentiation of HepG2 cells induced by retinoic acid determined resistance to GEL and GES treatments without the activation of JNK signaling pathway. Overall, the results obtained indicate that water-soluble garlic extracts are more inhibitory of the growth of transformed hepatoma cells than the oil-soluble isolated compound DADS, and that their antiproliferative properties are different depending on the area of origin of the starting material.

Prevalence of obesity and association with ischemic stroke in elderly subjects

Stroke is a leading cause of mortality and subsequent serious long-term physical and mental disability among elderly. While evidence suggests that obesity has an independent relation to coronary disease, similar findings for stroke have not been established. The purpose of this study was to examine the relation between body mass index (BMI) and ischemic stroke in elderly subjects over 65 years.
A population based, incident case-control study was conducted in Rome, Italy. Cases of first ischemic stroke admitted to rehabilitation centre were enrolled from Nutristroke randomized controlled trial and matched by age, sex and main stroke risk factors (hypertension, diabetes and smoking status) to stroke-free community control We conclude that elevated BMI (stronger among females) was associated with an increased risk for ischemic stroke, especially in elderly females. The result supports the statement that obesity prevention and weight reduction need greater emphasis in stroke prevention programs and the role BMI as a risk factor later in life.

Neolithic transition: nutritional meaning in human evolution

The introduction of agriculture and animal husbandry 10000 years ago produced profound changes in human culture, lifestyle and diet. In a relatively short time for metabolic adjustment, Palaeolithic food from wild animals and plants was replaced by the meat of domesticated animals having different fat composition, and by cereals, providing high amounts of readily available energy from carbohydrates. Combined with more sedentary life styles, this may have been a major source of epidemically expanding metabolic diseases.

De Martino A., Filomeni G., Aquilano K., Ciriolo M.R., Rotilio G. 2006. Effects of water garlic extracts on cell cycle and viability of HepG2 hepatoma cells. J Nutr Biochem. Nov;17(11):742-9.

Cairella G., De Martino A., Garbagnati F., Mistura L., Multari M., Sgognamiglio U., Venturiero V., Paolucci S. 2006. Prevalence of obesity and association with ischemic stroke in elderly subjects
JNHA – The Journal of Nutrition, Health & Aging, 10-1; 74-75.

Rotilio G., Marchese E. 2008. "Il significato nutrizionale della transizione neolitica nell'evoluzione umana" MUNDUS, Anno I numero I gennaio-giugno. G.B. Palumbo & C. Editore S.p.A. Palermo.

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■ **PHD STUDENTS** Sara Baldelli • Sara Piccirillo ■ **TECHNICAL ASSISTANT** Patrizia Civitareale

Biochemical mechanisms of glutathione novel functions

Palamara A.T., Nencioni L., Aquilano K., De Chiara G., Hernandez L., Cozzolino F., Ciriolo M.R. and Garaci E. 2005. Inhibition of influenza A virus replication by resveratrol. J.Infect. Dis. 191, 1719-1729.

Filomeni G., Aquilano K., Rotilio G. and Ciriolo M.R. 2005. Anti-apoptotic response to buthionine sulfoximine-dependent cytochrome c release: putative involvement of heat shock proteins and NF-kB. Antiox.Redox Signal 7, 444-453.

Filomeni G., Aquilano K., Civitareale P., Rotilio G. and Ciriolo M.R. 2005. Activation of c-jun-N-terminal kinase is required for apoptosis triggered by glutathione disulfide in neuroblastoma cells. Free Rad.Biol.Med. 39, 345-354.

Filomeni G., Aquilano K., Rotilio G. and Ciriolo M.R. 2005. Glutathione-related systems and modulation of extracellular signal-regulated kinases are involved in resistance of AGS adenocarcinoma gastric cells to diallyl disulfide-induced apoptosis. Cancer Res. 65, 11735-11742.

Ciriolo M.R. 2005. Redox control of apoptosis. Antiox.Redox Signal 7, 430-433.

Glutathione is a pivotal constituent of antioxidant defence and enzyme cofactor involved in the maintaining of intracellular redox environment.
Under physiological conditions it is easily oxidized and rapidly regenerated by redox reactions either directly or by several enzymes (e.g. glutathione peroxidase, glutathione reductase). This characteristic allows glutathione to play an essential role in many biochemical and pharmacological reactions, so acting as reducing and antioxidant agent, especially in the metabolism of different cell molecules and xenobiotics. Today additional implication of glutathione has been recognized: in fact, glutathione can modulate the immune responses, participate in gene expression and regulation of the activity of sulfhydryl-containing proteins either via thiol-disulfide exchange reactions or by the reduction of potentially toxic peroxides. Moreover, GSH is involved in the mitochondrial mechanisms that link opening of the permeability transition pore complex and activation of cell death by apoptosis. The GSH/GSSG ratio also profoundly modulates cell signalling and the MAPK-mediated phosphorylative cascade essential for cell cycle regulation and cell death. Our studies have contributed to the discovery of additional physio-pathological roles of glutathione such as:
Regulation of viral replication. We have shown that the life cycles of several viruses are influenced by host-cell redox states, and that antioxidants strongly inhibit the replication of the influenza virus. Glutathione is decreased by both virus infection and replication, and compounds that inhibit such alteration (e.g resveratrol) are able to significantly improve survival and also decrease pulmonary viral titers in influenza virus-infected mice.
Transduction of redox signal across the cell membrane. Changes in the intracellular reduced/oxidized glutathione ratio (GSH/GSSG) are crucial events that trigger downstream proliferation or death responses. We have investigated the molecular mechanisms underlying redox-mediated cell signalling upon extracellular oxidative insult. This challenge results in a significant decrease of exofacial cell membrane thiol groups and intracellular decrement of GSH content, owing to its engagement in the formation of mixed disulfides. The consequent intracellular redox unbalance gives rise to ROS production and activation of cell-type specific MAPK-mediated signalling pathways that ultimately could result in the commitment to apoptosis.
c) *Modulation of apoptotic processes*. Depending on the cell type and the protein machinery recruited, redox unbalance can eventually induce different signalling routes, in turn resulting in opposite demises: apoptotic death or anti-apoptotic response. In this context, we have demonstrated that formation of protein mixed disulfides with glutathione is a causative event in development of cell resistance to redox apoptotic stimuli. Moreover, we have also shown that glutathione is fundamental in preventing cytochrome *c* release from mitochondria. Unexpectedly, this event was not sufficient to trigger apoptosis in tumour cell-types equipped with high levels of hsp27/hsp70 system, which is responsible for cytosolic cytochrome *c* clearance.

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Oxidative stress and modulation of redox signalling for cancer treatment

Oxidative stress, due to either an increase in the oxidizing species or to a decrease in the antioxidants, plays a fundamental role in the regulation of several cellular processes associated with growth, differentiation and death. Indeed, several kinases and nuclear transcription factors are sensitive to redox-mediated regulation. Moreover, recently, modifications of the redox state of cysteine residues of certain proteins, which is a widespread mechanism in the regulation of protein function, has been proposed as being involved in signaling pathways. In particular, the pathways regulated by the mitogen activated protein (MAP) kinases represent well-established examples of the cross talk between redox-mediated signaling and phosphorylative cascades. Growing evidence suggests that cancer cells are under increased oxidative stress compared to normal cells. This condition leads to oncogene mutation and uncontrolled cell proliferation. Furthermore, cancer cells are often infiltrated with inflammatory phagocytes, which can generate large amounts of ROS within the tumour tissue. Cancer cells require high levels of ATP supply to maintain uncontrolled proliferation. This incessant energy demand leads to high glycolytic activity and lactate production and overload of mitochondrial respiration, overall contributing to increase ROS concentration. Oxidative stress in cancer cells may have significant consequences, such as alterations in cellular sensitivity to anticancer agents and occurrence of resistance. Nevertheless, some cancer types are equipped with a less efficient antioxidant defence system with respect to normal cells. Such a feature has been exploited to selectively kill malignant cells by redox-active chemotherapeutics. In particular, signalling pathways mediated by the pro-apoptotic members of MAPK family, JNK and p38 MAPK, seem to be profoundly involved in the activation of cell death processes of tumor histotypes downstream of chemotherapeutics-induced oxidative conditions. In this context, the main goal of our research has been to identify the redox-dependent molecular mechanisms underlying tumour cell death in order to delineate efficient anticancer strategies. In particular, we have developed promising redox-based chemotherapeutic molecules containing copper, which selectively target nuclear and mitochondrial compartment in a manner resembling that of delocalized lipophilic cations, promising class of molecules for cancer treatment. A novel glutathione-S-transferase (GST) inhibitor, NBDHEX, has been also designed to selectively kill tumor cells, by allowing the detachment of JNK from GST in a redox-independent manner. To corroborate the promising use of NBDHEX as chemotherapeutic, we have also demonstrated that it efficiently overcomes multidrug resistance (MDR) in different resistant tumor cells expressing both MDR protein and P-glycoprotein-mediated export systems.

Filomeni G., Rotilio G. and Ciriolo M.R. 2005. Disulfide relays and phosphorylative cascade: partners in redox-mediated signaling pathways. Cell Death Differ. 12, 1555-1563.

Turella P., Cerella C., Filomeni G., Bullo A., De Maria F., Ghibelli L., Ciriolo M.R., Cianfriglia M., Mattei M., Federici G., Ricci G. and Caccuri A.M. 2005. Pro-apoptotic activity of new glutathione S-transferase inhibitors. Cancer Res. 65, 3751-3761.

Turella P., Filomeni G., Dupuis M.L., Ciriolo M.R., Molinari A., De Maria F., Tombesi M., Cianfruglia M., Federici G., Ricci G. and Caccuri A.M. 2006. A strong glutathione S-transferase inhibitor overcomes the P-glycoprotein mediated resistance in tumor cells. NBDHEX triggers a caspase-dependent apoptosis in MDR1-expressing leukemia cells. J Biol Chem. 281.

Filomeni G., Cerchiaro G., Da Costa Ferreira A.M., De Martino A., Pedersen J.Z., Rotilio G. and Ciriolo M.R. 2007. Pro-apoptotic activity of novel isatin-Schiff base copper(II) complexes depends on oxidative stress induction and organelle-selective damage. J.Biol.Chem. 282, 12010-12021.

Filomeni G., Graziani I., Rotilio G. and Ciriolo M.R. 2007. trans-Resveratrol induces apoptosis in human breast cancer cells MCF-7 by the activation of MAP kinases pathways. Genes Nutr. 2, 295-305.

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■ **PHD STUDENTS** Sara Baldelli • Sara Piccirillo • Paola Vigilanza • Simone Cardaci ■ **TECHNICAL ASSISTANT** Patrizia Civitareale

Oxidative stress, aging and neurodegenerative diseases

Aquilano K., Vigilanza P., Rotilio G. and Ciriolo M.R. 2006. Mitochondrial damage due to SOD1 deficiency in SH-SY5Y neuroblastoma cells: a rationale for the redundancy of SOD1. FASEB J. 20, 1683-1685.

Aquilano K., Filomeni G., Baldelli S., Piccirillo S., De Martino A., Rotilio G. and Ciriolo M.R. 2007. Neuronal nitric oxide synthase protects neuroblastoma cells from oxidative stress mediated by garlic derivatives. J.Neurochem. 101, 1327-1337.

Vigilanza P., Aquilano K., Rotilio G. and Ciriolo M.R. 2007. Transient cytoskeletal alterations after SOD1 depletion in neuroblastoma cells. Cell.Mol. Life Sci. 65, 991-1004.

There are several observations suggesting that the brain may be particularly vulnerable to oxidative stress. Some of the most important are: (i) The brain has a high aerobic metabolism that inevitably leads to ROS formation *via* oxygen reduction. (ii) The cerebrospinal fluid contains small molecular weight iron and copper complexes, which catalyze the formation of the highly reactive hydroxyl radicals. It is poor in the antioxidants, transferrin, and ceruloplasmin, which normally bind to and segregate these transition metals. (iii) The release of excitatory neurotransmitters, such as glutamate, dopamine and nitric oxide, induces a cascade of reactions resulting in the formation of ROS. (iv) The brain contains low levels of antioxidants (e.g. catalase, glutathione peroxidase, vitamin E), as compared to other tissue such as liver and they undergo to progressive reduction during life. (v) Neurons are non-replicating cells and any damage to brain tissues by the ROS tends to be cumulative over time. All these observations support the hypothesis that mitochondrial dysfunction, oxidative stress, and decreased metabolism may be a common pathway to several neurodegenerative conditions, including normal aging of the brain. It has been proposed that age-related decline in mitochondrial function due to oxidative stress plays an important role in the functional impairments that occur in the aging of the brain and in age-associated neurodegenerative disorders. In this context, our research focused on the molecular mechanisms linking oxidative/nitrosative stress and ageing or neurodegeneration. Particularly, we dissected the mechanisms by which the antioxidant cytosolic enzyme copper, zinc superoxide dismutase (SOD1) can maintain both mitochondrial and cytoskeletal homeostasis of neuronal cells.
We characterized the molecular pathways following SOD1 impairment and the consequent superoxide-mediated stress, identifying glutathione as an alternative molecule for superoxide buffering. Moreover, we identified a functional relationship of SOD1 with p38 MAPK and Bcl-2 essential for preventing cytoskeletal and mitochondrial impairment respectively. Finally, we demonstrated that a garlic-derived compound, diallyl disulfide (DADS), which usually exerts pro-oxidant effects, is an efficient inducer of neuronal nitric oxide synthase.
The DADS-mediated NO production was not cytotoxic but instead significantly reduced intracellular ROS production and apoptotic cell death. These results are of particular interest because they could provide a rationale for the beneficial health effects of garlic and at the same time allow us to postulate the possible use of DADS as a protective factor in pathologies of the nervous system associated with impairment of NO synthesis by neuronal NO synthase.

GROUP LEADER Luisa Rossi ■ **PHD STUDENT** Mario Arciello ■ **TECHNICAL ASSISTANT** Concetta R. Capo

Alteration of copper homeostasis and neurodegeneration

The impairment of the homeostasis of the essential transition metal ion copper (resulting in either the deficit or excess or aberrant coordination or distribution of the metal) is deleterious to neuronal cells, possibly due to oxidative stress. Indeed, the brain shows high levels of copper in comparison with other organs. Therefore it is particularly at the risk if copper homeostasis fails. In Wilson's disease, a genetic impairment of copper efflux, increased levels of the metals are associated with neurodegeneration. In order to understand the molecular mechanisms underlying copper toxicity, we set up a cell model for this disease, where we found that copper mainly accumulates in mitochondria, induces metabolic arrest and cell death due to the production of reactive oxygen species and impairment of mitochondrial proteins, mainly complex I of the respiratory chain.
Many neurodegenerative diseases are typical of the elderly and it is not unlikely that, during aging, the control over copper homeostasis undergoes progressive failure, thus resulting in the alteration of the copper burden in the aged brain. Alzheimer's disease (AD) is the major neurodegenerative disease of the aging brain, associated with progressive memory loss and cognitive impairment, as a result of neuron demise, characterized by the accumulation in the brain of senile plaques formed by the fibrillation of the Aβ, polypeptide. Mounting evidence suggests that copper is intriguingly connected with the established molecular markers of AD, and that copper homeostasis is disturbed in affected individuals, leading to oxidative stress and neurodegeneration. One of the main goals in AD studies is the identification of blood markers to aid diagnosis and monitor the effects of therapeutic approaches. In recent years our laboratory has been involved in a series of studies on AD patients, in order to assess whether alterations of copper homeostasis may represent a marker of AD in tissues other than the brain. We aimed at identifying these alterations in serum, given that copper concentration in the brain depends on circulating copper levels, and tried to verify if it could be representative of the clinical status of the patients. Particularly, we have been focusing on the serum copper-binding protein ceruloplasmin.
By calculating the ratio between copper and ceruloplasmin, we could distinguish two pools of copper, related and unrelated to ceruloplasmin. Using statistical analyses, we found that the pool of copper unexplained by the protein best characterizes AD patients and could thus be proposed as a putative marker for an early diagnosis of this disease. It is conceivable that this fraction of copper can easily cross the blood-brain barrier and feed the brain with a continuous flux of noxious redox copper, which in AD might play a role in Aβ-mediated toxicity to the brain.

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Molecular mechanisms of neurodegenerative diseases

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Mostly because of the increase in life expectancy, adult-onset neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS) and others are becoming a major health and social problem in developed countries. It is estimated that 4.5 million Americans suffer from AD and about 1 million Americans suffer from PD, while 5,000 new ALS cases are diagnosed each year in U.S.A alone. To date, no effective therapy is known for these diseases; this is mostly due to the fact that the molecular mechanisms underlying neurodegenerative disorders are still obscure.

A common theme in neurodegeneration is mitochondrial damage. We have contributed to this field with several studies. Using cell and animal models for familial ALS linked to point mutations in the gene coding for SOD1, we have demonstrated that mitochondrial dysfunction derives directly from the association of the mutant SOD1 with these organelles. Such association causes a decrease in the respiratory function and appears to be specific for motoneuronal cells, i.e. those cells that are mostly affected and die in ALS patients (1). We have also demonstrated that the mitochondria-mediated apoptotic pathway in ALS is activated through Bcl2a1, a member of the Bcl2 family of proteins that serves as a switch in death of motor neurons (2). Since genetic ablation of Apaf1 prevents SOD1-induced neuronal degeneration, this death pathway depends also on the presence of a functional apoptosome (3).

A similar, mitochondria-mediated, death pathway seems to take place in PD, at least in those patients that carry mutations in the gene coding for LRRK2, a mitochondria membrane-associated protein that is predominantly expressed in dopaminoceptive areas of the brain and whose function is still quite obscure. We have discovered that mutant LRKK2 is able to induce death of neuronal cells through the Apaf1/caspase3 pathway, mediated by the LRR or WD40 domains of LRRK2 (4).

Mitochondrial dysfunction may induce neuronal death directly, as in the case of ALS, or through more complex mechanisms. Indeed, we have obtained indications that mitochondrial damage modulates alternative splicing in neuronal cells, increasing the levels of less-represented isoforms of many mRNAs, including those coding for some proteins involved in apoptosis (5).

Apoptotic death may be induced in hippocampal neurons through a further mechanism. Using neuronal cultured cells treated with the $A\beta_{1-42}$ peptide, APP_{SWE}//AChE- transgenic mice and post-mortem frontal cortex samples from AD patients, we have observed that oxidative stress, possibly arising from mitochondrial damage, modulates calcineurin, a protein phosphatase involved in a number of pathways crucial for neurons, including cytoskeletal disorganization, calcium handling and signalling for apoptosis (6).

Taken as a whole, these pre-clinical studies represent a contribution to the individuation of targets for novel therapeutic approaches.

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Structure and function of mitochondrial carriers

The transport of various metabolites and cofactors across the inner mitochondrial membrane is essential for eukaryotic metabolism and is accomplished by a family of nuclear encoded transporters, the mitochondrial carrier family. The genome of eukaryotes encodes typically between 35 and 55 different carriers, sharing common features such as a tripartite structure made up of three tandemly repeated sequences of about 100 amino acids in length, the presence of six putative a-helical transmembrane segments connected by hydrophilic loops, and the presence of a conserved PX(-)XX(+)X(+) sequence, known as "mitochondrial carrier signature" or MCS motif, that is located in the C-terminal part of the odd-numbered helices.

In our laboratory we are interested in understanding the structural and functional properties of this class of enzymes studying them trough experimental and computational approaches. In this period we have characterized the occurrence of specific conformational changes in the oxoglutarate carrier, necessary for the transport of the substrate, following the variation of the fluorescente spectrum of single tryptophan residues selectively introduced at definitive position of the transmembrane segments by site-directed mutagenesis (1). Moreover we have described the structure of the VI transmembrane segment of the same carrier using site directed spin labeling (SDSL), a technique that combines site directed mutagenesis and EPR (electron paramagnetic resonance) spectroscopy. The general strategy of SDSL is to introduce a nitroxide side chain (the spin label) via single cysteine substitution mutagenesis followed by modification of the unique sulfhydryl group with a specific nitroxide reagent, and take advantage of the wealth of information in the EPR spectrum of the nitroxide to define variables that characterize the local environment of the side chain. From the EPR spectrum we have evaluated three primary parameters, namely solvent accessibility, local mobility and a polarity index that has made it possible to build the topography of the secondary structure of the VI transembrane segment with respect to the membrane surface and propose a model structure at the backbone level (2).

From the simulative point of view we have used molecular molecular dynamics simulations to investigate the structural-dynamical properties of the ADP/ATP carrier and evidentiate the crucial role of three proline residues present in the odd transmembrane segments to induce the presence of the conformational changes necessary in the transport process. The study has also shown the importance of charged residues in the stabilization of different conformations through the occurrence of specific salt bridges (3). Finally the interaction of the three main components of the mitochondrial membrane, namely cardiolipin, phosphatidylcholine, and phosphatidylethanolamine, has been studied by atomic force microscopy (AFM) measurements indicating the presence of two domains: one made by phosphatidylethanolamine and the other by a regular arrangement of phosphatidylethanolamine and cardiolipin at a fixed molecular ratio (4).

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Interaction of human topoisomerase I with the camptothecin anticancer family drugs

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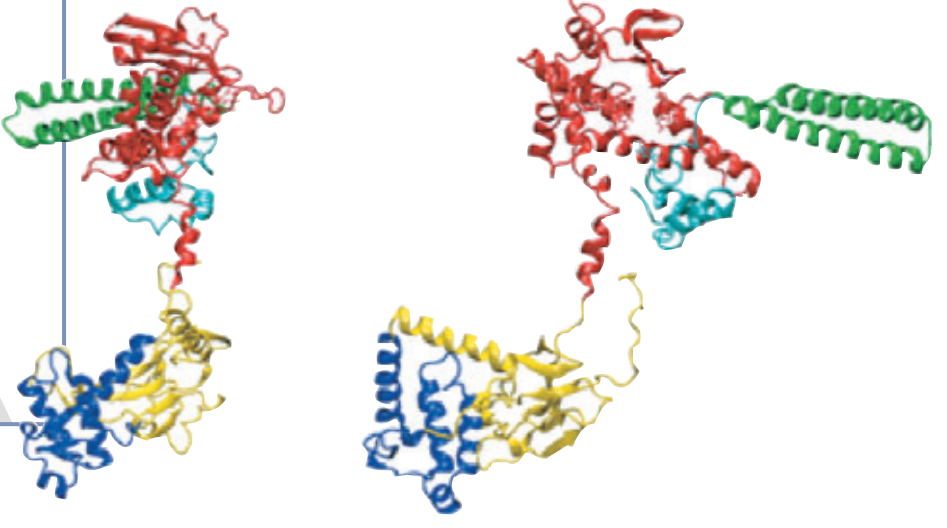
DNA topoisomerases are enzymes that control and modify the topological states of DNA in cells. Human topoisomerase I is composed of 765 aminoacids, divided into four different domains: N-terminal domain (amino acids 1-206),core domain (aminoacid 207-635), linker domain (636-712), and C-terminal domain (amino acids 713-765). The catalytic cycle is composed of five subsequent steps: binding of the enzyme to DNA; DNA cleavage; controlled rotation of the DNA scissile-strand; DNA religation; DNA release. During these steps the enzyme undergoes large conformational variations, passing from an "open" structure that allows the DNA binding, to the "close" conformations observed by X-ray diffraction. Human topoisomerase I is of significant medical interest, since it is the only target of the antitumor drug of the camptothecin (CPT) family, two of them topotecan and irinotecan being in clinical use for many solid tumors. CPT reversibly binds to the covalent intermediate DNA-enzyme, stabilizing the cleavable complex and reducing the rate of religation. The stalled topoisomerase I collides with the progression of the replication fork producing lethal double-strand DNA breaks and cell death. In our laboratory we are interested in the characterization of the mechanism of action of this enzyme and in the elucidation of the principles governing the drug interaction in order to develop more efficient drugs. In this period we have investigated mutants displaying drug-resistance correlating their structural dynamical properties with their varied function and their different sensitivity to the drug (1,2). We have also carried out a detailed investigation of the electronic properties of the topotecan drug (3), as a first step toward a deep and accurate description of the drug interaction with the binary enzyme-DNA complex. Finally we have provided for the first time the description of the structure of the enzyme in its open conformation ready to interact with the supercoiled DNA substrate (4) and figure 1.



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Human Glutathione Transferase P1-1 may act as an effective target for some antitumor drugs

Human Glutathione Transferase P1-1 (GST P1-1) belongs to a superfamily of enzymes which play an important part of a coordinated antioxidant response system GSH-mediated. Beside its well known catalytic role in the detoxification processes, recent advances suggest new functions, such as, stress response, apoptosis, oncogenesis and drug resistance. Human GST P1-1 has been strongly implicated in many solid tumors and is often overexpressed following exposure to anti-tumor drugs. The acquired resistance which eventually arises in patients, after an initial period of successful treatment, has been related in some cases to the presence of this enzyme. GST P1-1 has also been proposed as a possible tumour marker for certain types of cancer (eg. prostate cancer), where its lack of expression is an unfavourable prognostic factor.

Our own studies on human GST P1-1 using site-directed mutagenesis and crystallographic analyses have identified residues involved in catalysis and in binding of substrates/inhibitors (eg. Cys 47 and Cys 101, Tyr 7, Tyr 49 and Tyr 108) as well as revealing the intrinsic flexibility of certain portions of the molecule (eg. regions lining the GSH binding site). We have, therefore, started a series of experiments with the aid of medicinal chemistry and crystallography to design optimal inhibitors for GST P1-1 with the aim of overcoming the acquired drug resistance. A series of organometallic ruthenium complexed with ethacrynic acid (EA) (a well known inhibitor of GST P1-1) were synthesized and tested against some tumor cell lines and the purified protein. These bifunctional inhibitors may be among the more effective modulators of GST P1-1 because they bind to the protein through a new mechanism i.e. there is binding of the ruthenium center at the dimer interface whilst EA binds at the enzyme's hydrophobic site (H-site), after cleavage of the parent EA-ruthenium compound at the dimer interface.

Our results show they are effective inhibitors of the growth of human ovarian cancer cell lines, irrespective of cisplatin resistance, and suggest that GST P1-1 is the possible target of these complexes in vitro.

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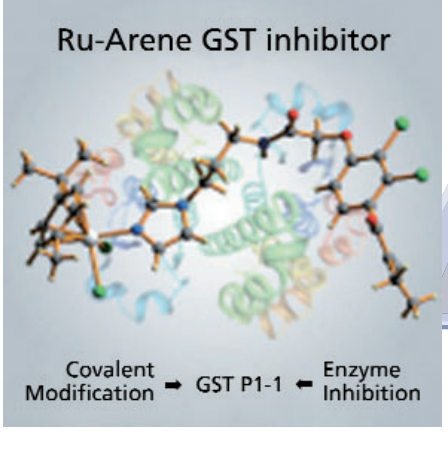
Organometallic Ruthenium Inhibitors of Glutathione-S-Transferase P1-1 as Anticancer Drugs



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Storage and transport of dinitrosyl iron complexes is mediated by glutathione transferases

Cesareo E., Parker L.J., Pedersen J.Z., Nuccetelli M., Mazzetti A.P., Pastore A., Federici G., Caccuri A.M., Ricci G., Adams J.J., Parker M.W., Lo Bello M. 2005. Nitrosylation of human glutathione transferase P1-1 with dinitrosyl diglutathionyl iron complex in vitro and in vivo. J.Biol.Chem. 280, 42172-42180.

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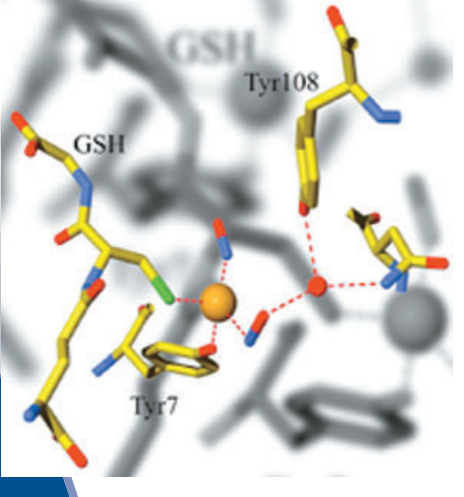
We have previously shown that human glutathione transferase P1-1 (GST P1-1), by means of an intersubunit communication, may act as a NO carrier while maintaining its well known detoxificating activity toward dangerous compounds. The binding of the dinitrosyl diglutathionyl iron complex (DNDGIC) with high affinity (K_d 10^{-7} to 10^{-10} M) has also been observed in the human Mu, Alpha and Theta GST classes suggesting a common mechanism by which GSTs may act as intracellular NO carriers or scavengers. A crystal structure of GST P1-1 in complex with the DNDGIC ligand at high resolution reveals that the active site Tyr-7 coordinates to the iron atom through its phenolate group by displacing one of the GSH ligands. Electron paramagnetic resonance spectroscopy studies on intact *Escherichia coli* cells expressing the recombinant GST P1-1 enzyme indicate that bacterial cells, in response to NO treatment, are able to form the DNDGIC using intracellular iron and GSH. The binding of DNDGIC to GST P1-1 is reversible (loss of EPR signal occurring within 1 hour) unless Fe is supplied as an external source. The specific interaction of DNDGICs with GSTs raises the question of their function and whether there could be an interaction with multi-drug resistance protein 1 (MRP1) by considering the known role of these proteins in the detoxification processes. Hence, it has been hypothesized GSTs may act as a physiological protective mechanism against the generation of high intracellular levels of DNDGICs. Consistent with this is the recent finding that 20% of DNDGIC-GST complex was found to be associated with the outer membrane of the nuclear envelope, suggesting a protective role against DNA damage.

Crystal structure of GST P1-1-DNDGIC complex



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Plasma membrane functions and signal transduction

The involvement of phospholipid-derived mediators, following the interaction of signalling effectors with the mammalian plasma membrane, has been investigated in cellular models such as Rat Aortic Smooth Muscle Cells (RASM cells) or a monocytic cell line (THP-1). In RASM cells, lysophosphatidic acid (LPA) induced cell growth and ROS production together with the activation of Akt, i.e.of a downstream target of phosphatidylinositol 3-kinase (PI3K): This effect was completely inhibited by physiological concentrations of the Atrial Natriuretic Peptide (ANP) which also inhibited p42/p44 phosphorylation. These data suggested that PI3K plays a pivotal role for the LPA signal transduction pathway, also acting as a target for the antiproliferative action of ANP. LPA was reportedly identified as a modulator of both proliferation and activation in different cell types involved in inflammation-associated pathologies. Work on THP-1 cells revealed that LPA significantly increased DNA synthesis and reactive oxygen intermediates production as well as prostaglandin release and LPA receptor upregulation. Another group of experiments has investigated how synaptic function is affected by altered dynamics of lipid microdomains after cholesterol depletion in the hippocampal region. As a matter of fact, several degenerative disorders were associated with an impaired cholesterol homeostasis, taken as granted that cholesterol acts on synaptic activity stabilizing membrane microdomains. Thus, the study was focused on the role exerted by cholesterol on the main neurotransmitter receptors involved in synaptic transmission and plasticity by using electrophysiological recordings in hippocampal brain slices treated by beta-cyclodextrin, a molecule able to dissolve the hydrophobic core of lipid rafts by cholesterol removal. Our main findings were that cholesterol depletion: (i) reduces, in a time-dependent way, basal synaptic transmission; and (ii) affects the induction and the maintenance of LTP possibly through the modulation of NMDA receptors. In another group of experiments we investigated how glycosphingolipids are involved in the regulation of cellular functions. It is well known that the glycosidic moiety of glycosphingolipids, particularly of gangliosides, may be involved in the recognition of other glycosilated molecules, either lipids or proteins, a relevant function for cell-to-cell or cell-to-substrate adhesion. Moreover, it is known that glycosphingolipids, as well as sphingomyelin and cholesterol, are major components of lipid rafts: i.e. plasma membrane domains characterized by low lipid fluidity, in which membrane proteins involved in signal transduction are permanently or transiently located. Current research is aimed at studying the possible role of glycosphingolipids as modulators of signal transduction operated by membrane receptors.

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Study of the mechanisms involved in inflammatory and excitotoxic-mediated neuronal injury and identification of potential targets for neuroprotection

1. Muscoli C., Visalli V., Colica C., Nisticò R., Palma E., Costa N., Rotiroti D., Nisticò G. and Mollace V. 2005. The effect of inflammatory stimuli on NMDA-related activation of glutamine synthase in human cultured astroglial cells. Neurosci Lett. 373,184-8.
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3. Nisticò R., Piccirilli S., Cucchiaroni M.L., Armogida M., Guatteo E., Giampà C., Fusco F.R., Bernardi G., Nisticò G. and Mercuri N.B. 2008. Neuroprotective effect of hydrogen peroxide on an in vitro model of brain ischaemia. Br J Pharmacol. 153,1022-9.

Glutamate excitotoxicity, oxidative stress and inflammation are primary mediators of neuronal death during ischemia and reperfusion. Approaches that inhibit one or more of these events have proved of therapeutic efficacy in preclinical studies, while producing discouraging results in clinical trials. Hence, the availability of drugs able to counteract stroke-induced neurodegeneration is still an urgent but unmet need. It is well known that astrocytes can influence in several ways the vulnerability of neurons to synaptically released glutamate. In fact, glutamate uptake by astrocytes normally prevents excitotoxic glutamate elevations in brain extracellular space, and this process appears to be a crucial determinant of neuronal survival in the ischemic penumbra. In particular, when glutamate is accumulated in massive amounts in the extracellular space, it can be taken up by astroglial cells and then converted into non-toxic glutamine by the glia-specific enzyme glutamine synthase (GS). In line with this, we have demonstrated that inflammatory cytokines can attenuate GS adaptive responses in astroglial cells, thus contributing to the potentiation of excitotoxic mechanisms driven by excessive amounts of glutamate in inflamed brain tissue (1). Other mechanisms triggered by episodes of energy failure include a sequence of early and delayed events that can lead to transient or permanent injury of neurons by affecting the cells' energy requirements, pump function or membrane integrity. Accordingly, oxygen/glucose deprivation (OGD) causes increased membrane permeability to sodium and calcium ions throughout voltage-dependent channels and ionotropic glutamate receptors. On the other hand, increased membrane permeability to potassium ions caused by the opening of K^+-ATP channels consequent to energy failure is believed to play a protective role, due to the limitation in cellular excitability. Nevertheless, on an in vitro model of brain ischemia, we demonstrated that the selective and rapid blockade of plasmalemmal ATP-sensitive potassium channels results in neuroprotection, an effect due to preservation of the Na^+K^+-ATPase pump activity (2). Beyond the involvement of voltage-dependent ion channels and ionotropic receptors at the synaptic level, also reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2), superoxide (O_2^-) and/or hydroxyl radical (OH^-), have been postulated as contributing to neuronal damage caused by hypoxia/reoxygenation. Nevertheless, recent data suggest that ROS and H_2O_2 have normal regulatory actions, playing a major role as important regulators of eukaryotic signal transduction in a variety of biological processes. Consistently, we have confirmed either physiological or protective roles of H_2O_2 in the brain on an in vitro model of oxygen/glucose deprivation (OGD) (3). We have also shown that its neuroprotective effect is mediated by the production of molecular oxygen through the catalase pathway, thus suggesting that pharmacological treatments designed to transiently increase the endogenous production of H_2O_2 below toxic levels, could represent a viable neuroprotective strategy in conditions of cerebral ischemia.

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■ **PHD STUDENTS** Samantha Virgili (Ancona) ■ **OTHER RESEARCHERS** Tiziana Duranti (Ancona) • Daniela Maraschio (Ancona)

Biophysics of nucleic acids and gene expression

Our background investigations showed that, although a slight extra-S phase asymmetric methylation occurs *de novo* on CpC/GpG, CpT/GpA and CpA/GpT dinucleotide pairs, a heavy methylation during S involves semiconservatively newly made chains to guarantee genetic *maintenance* of 5-methylcitosine (m^5C) in symmetrically dimethylated m^5CpG/Gpm^5C dinucleotide pairs. Probes of methylated DNA helped to discover, in the eukaryotic gene, the presence of methylated sequences that do not code for mRNAs and an inverse correlation was detected between DNA methylation, in S, and RNA transcription, in G_1 and G_2. This basic rule was confirmed by the fact that in lymphocytes (where the *hTGc* gene is inactive) its promoter shows two fully methylated CpG-rich domains at 5' and one fully unmethylated CpG-rich domain at 3' including the site +1 and a 5'-UTR, whereas in *Huvec* cells (where the *hTGc* gene is active) in the first CpG-rich domain of its promoter four CpGs appear to lack $–CH_3$: a result stimulating hypotheses on the machinery of transcription (1).
Thus, while a number of data collected in 2005-2007 accounted for genome stability in *Friend erythroleukemia* cells *vs*. deprivation or enrichment of the geomagnetic field (2), attention was paid to a basic aspect of molecular evolution. In mammals, the pathways leading to synthesis and post-synthetic modification of DNA use methionine as common donor of atoms, since the carbon coming from the methyl group of this amino acid is necessary for replication and the entire methyl group is necessary to build m^5C on daughter strands (*FEBS-Lett. 44, 121-126, 1974*). In bacteria, an enzyme system construct (5) on DNA 6-methylaminopurine (m^6A) in addition to m^5C. The formation rate of m^6A – lost in mammals – gradually decreases during the bacterial culture growth cycle and that of m^5C reaches an optimum in its middle because the *dcm* and *dam* methyltransferase activities, as well as the activities of the methyltransferase moieties of the restriction-modification enzymes, are uncoupled (3). On the other hand, the Shine-Dalgarno hybrid found in *E. coli* during initiation of translation and elongation (4) suggested that polygenic messenger RNA modulates the rate of its proper translation through conformational changes (4), whilst in a Space-simulating magnetically shielded environment eukaryotic translation is slightly influenced by weak magnetic forces (5). Evaluated together, these facts contributed to shed some new light on the mechanisms regulating, in evolution, the response of biological targets of various orders of complexity to radiation (6).

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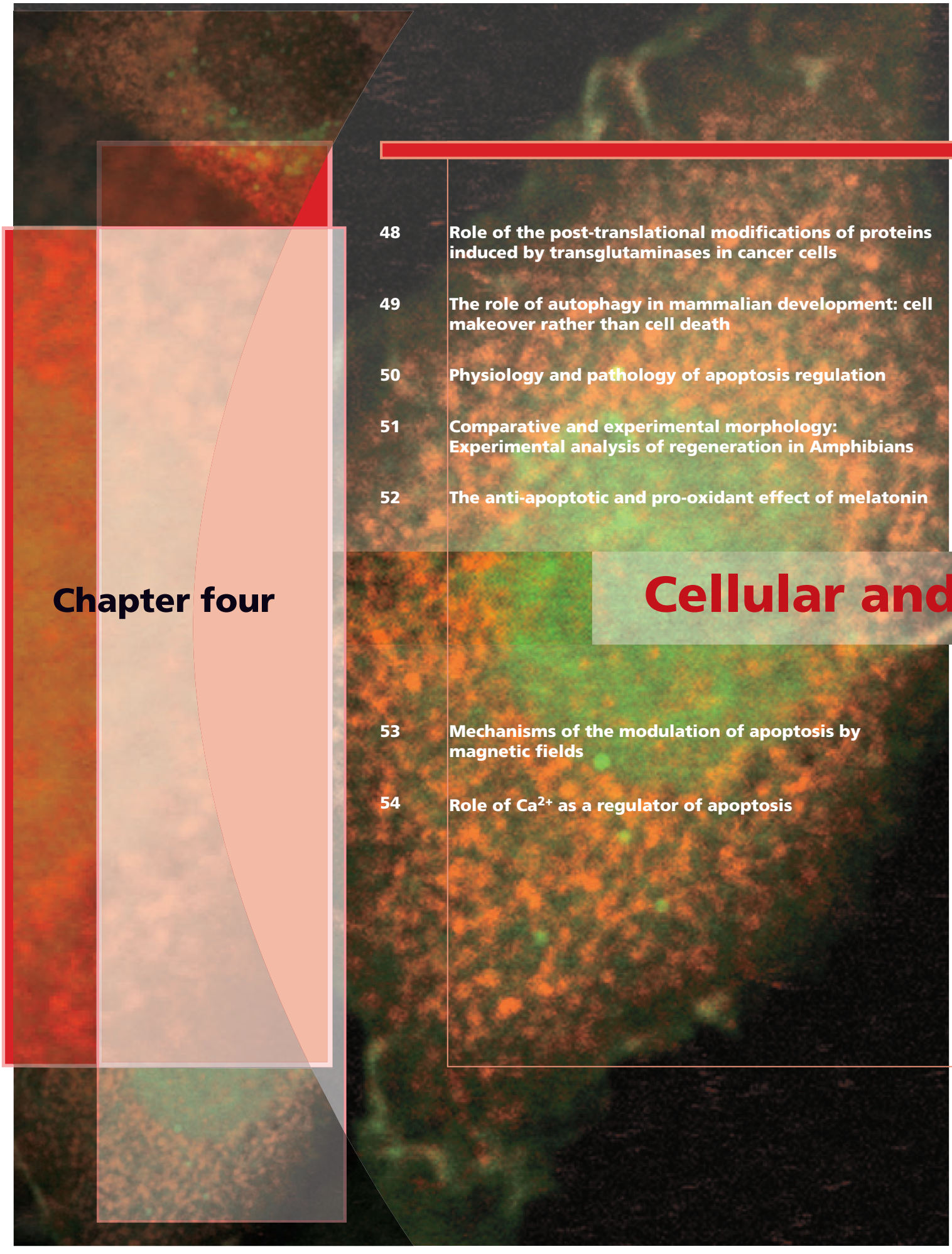
4. Volpe P. and Eremenko T. 2005. Gene Expression in a Space-simulating Magnetically Shielded Environment. Environmentalist 25, 83-92.
5. Maraschio D., La Teana A. and Volpe P. 2007. The Shine-Dalgarno hybrid during initiation of translation and elongation. Biopol. Cell 23, 243-249.
6. Volpe P. and Eremenko T. 2007. Mechanisms of the target response to magnetic fields and their correlation with the biological complexity. Environmentalist 27, 387-393.



Chapter four

Cellular and

Developmental Biology

GROUP LEADER Simone Beninati ■ **PHD STUDENT** Claudio Tabolacci ■ **TECHNICAL ASSISTANTS** Alessandro Lentini • Palma Mattioli • Bruno Provenzano

Role of the post-translational modifications of proteins induced by transglutaminases in cancer cells

Baldini P.M., De Vito P., Lentini A., Mattioli P., Provenzano B., Vismara D. and Beninati S. 2006. Decrease of polyamine levels and enhancement of transglutaminase activity in selective reduction of B16-F10 melanoma cell proliferation induced by atrial natriuretic peptide (ANP). Melanoma Res. 16(6): 501-507.

Bjelakovic G., Beninati S., Pavlovic D., Sokolovic D., Stojanovic I., Jevtovic T., Bjelakovic G.B., Nikolic J. and Basic J. 2007. Selenomethionine induces polyamine biosynthesis in regenerating rat liver tissue. Amino Acids 33: 525-529.

Costantino M., Caraglia M., Beninati S., Giuberti G., D'Alessandro A., Lentini A., Abbruzzese A., Bove G., Landolfi F., Rossi F. and Lampa E. 2005. Alternative therapy of old earth elements increases the chondroprotective effects of chondroitin-sulfate in mice. Exp. Mol. Medicine 37(5): 476-481.

Lentini A., Mattioli P., Provenzano B., Abbruzzese A., Caraglia M. and Beninati S. 2007. Role of the FAD-dependent polyamine oxidase in the selective formation of N^1, N^8-bis(γ-glutamyl)spermidine protein cross-links. Biochem. Soc. Trans. 35(part 2): 396-400.

Lentini A., Forni C., Provenzano B. and Beninati S. 2007. Enhancement of transglutaminase activity and polyamine depletion in B16-F10 melanoma cells by flavonoids naringenin and hesperitin correlate to reduction of the in vivo metastatic potential. Amino Acids 32: 95-100.

Nikolic J., Stojanovic I., Pavlovic R., Sokolovic D., Bjelakovic G. and Beninati S. 2007. The role of L-arginine in toxic liver failure: interrelation of arginase, polyamine catabolic enzymes and nitric oxide synthase. Amino Acids 32: 127-131.

The correlation between metastatic power of cancer cells and post-translational modification of protein appears to be supported by our recent findings.
We reported that a class of natural compounds known as methylxanthines, are able to increase soluble transglutaminase activity of cancer cells affecting their metastatic potential. The in vivo capacity of methylxanthine to influence B16-F10 melanoma cells metastatic behavior was investigated by injecting methylxanthine-treated melanoma cells into the bloodstream of syngeneic mice (C57BL6/N). We found an impaired ability of theophylline-treated cells to invade the target organ with a frequency of metastatic foci lowered of about 70% when compared with the control experiment. We are publishing a new procedure employing the integrated image analysis of the hystological section of invaded target organ, performed in the computerized image analysis center of our university, for the *in vivo* evaluation of the inhibitory effect of a drug on invasiveness and proliferation of murine melanoma cells. The mechanism of action of methylxanthines in cancer growth and metastasis is unknown. Our recent findings obtained by the new procedure of image analysis suggest that theophylline, and to an extent caffeine, possess two dominant effects on B16-F10 cells. One had a role in the overall inhibition of invasion, which affects the implantation of tumor cell in the target organ, and the second, shared with the other methylxanthines investigated, was involved in the reduction of the growth of melanoma cells in the colonized organ, likely through the induction of differentiation. Studies are in progress in order to include methylxanthines in the list of differentiation agents for cancer therapy. In fact, the role of methylxanthines, in particular for theophylline, in the control of melanoma progression in vivo, has been investigated by injecting melanoma cells into syngeneic mice treated with the drug. The results demonstrated a remarkable reduction of the frequency of the lung and liver metastases, as well as a significant increase in the lifespan of the treated animals, compared to the control ones. Furthermore, the direct involvement of transglutaminase in the antineoplastic effect has been recently demonstrated by treating mice with a plasmid containing the gene sequence for the enzyme. These preliminary experiments showed that the number of melanoma foci in the lung, related to tumor cell invasiveness, was considerably decreased in the treated animals, whereas the metastases size, related to cell proliferation, was unchanged, suggesting a strong anti-invasive rather than antiproliferative effect of transglutaminase activation.

GROUP LEADERS Francesco Cecconi • Mauro Piacentini ■ **POSTDOC** Sabrina Di Bartolomeo ■ **PHD STUDENTS** Claudia Fuoco • Luigi Giunta ■ **UNDERGRADUATE STUDENTS** Francesca Nazio • Giovanni Marchetti • Manuela Antonioli • Gabriella Bellavia ■ **COLLABORATOR** Gian Maria Fimia

The role of autophagy in mammalian development: cell makeover rather than cell death

Autophagy is an important cellular pathway for the degradation of bulk cytoplasm, long-lived proteins and entire organelles. Its molecular understanding began slightly more than a decade ago in yeast and since then several autophagy genes have now been cloned, functionally characterized and targeted in mice. The significance of autophagy in the physiology and pathology of adult tissues is being investigated in-depth, due to the clear involvement of autophagy in cancer, neurodegeneration, aging, infectious diseases and immunity. A role during development for autophagy as a cell death mechanism or as a stress response has also been described in lower eukaryotes. However, autophagy's significance in vertebrate development remains unexplained, as does the role (if any) of vertebrate-specific factors in its regulation. A careful analysis of the autophagy gene mutant mouse models generated thus far leads us to hypothesize that autophagy may be involved in mammals in specific cytosolic rearrangements needed for proliferation, death, and differentiation during embryogenesis and postnatal development. Thus, autophagy is a process of cytosolic 'renovation', crucial in cell fate decision.

In this context of studies, we have recently identified a novel Beclin 1-interacting protein, Ambra1, which is a positive regulator of the Beclin 1-dependent program of autophagy. Beclin 1 is the mammalian ortholog of yeast Autophagy gene 6 (Atg6), a component of the class III phosphatidylinositol-3-OH kinase (also known as Vps34) complex regulating autophagosome formation in mammals. Ambra1 functional deficiency in mouse embryos leads to neuroepithelial hyperplasia associated with autophagy impairment and accumulation of ubiquitinated proteins. Moreover, inhibition of proliferation by Ambra1 is dependent on Beclin 1, suggesting that autophagy dysregulation is mechanistically linked to abnormal cell proliferation. The discovery of a tuned control of basal autophagy for regulating the correct morphogenesis and cell number in the developing CNS, may reveal novel target factors for diagnostic and therapeutic purposes. Similarly, there is a need to further evaluate the contribution in humans of autophagy dysregulation in early developmental defects. The landmark discovery of the roles which autophagy plays in development may also have implications for cancer. In light of autophagy's role in tumorigenesis, it may be possible to pinpoint single components of the autophagy pathway that characterize, when mutated, the embryonic origin of various tumors.

Fimia G.M., Stoykova A., Romagnoli A., Giunta L., Di Bartolomeo S., Nardacci R., Corazzari M., Fuoco C., Ucar A., Schwartz P., Gruss P., Piacentini M. and Cecconi F. 2007. Ambra1 regulates autophagy and development of the nervous system. Nature 447, 1121-1125.

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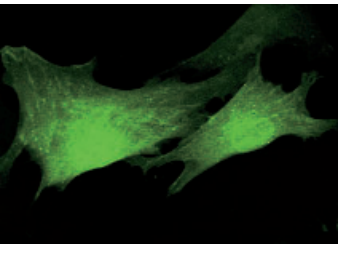
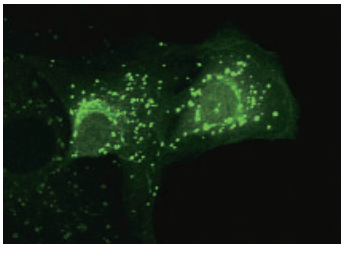
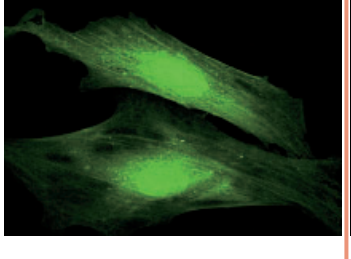
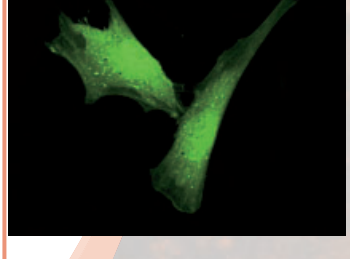
Ferraro E. and Cecconi F. 2007. Autophagic and apoptotic response to stress signals in mammalian cells. Archives of Biochemistry and Biophysics 462, 210-219.

Moreno S., Imbroglini V., Ferraro E., Bernardi C., Romagnoli A., Berrebi A.S. and Cecconi F. 2006. Apoptosome impairment during development results in activation of an autophagy program in cerebral cortex. Apoptosis 11, 1595-1602.

Ambra1 is a key factor in mammalian autophagy. Rapamycin is an inhibitor of mTOR, the upstream repressor of autophagy within the cytosol. When control cells (mouse embryonic fibroblasts) are treated by Rapamycin, autophagosomes are suddenly formed, as revealed by the LC3 green punctate staining (second panel from left). When Ambra1 is inactivated, autophagy does not occur upon Rapamycin stimulation.

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Physiology and pathology of apoptosis regulation

Corvaro M., Fuoco C., Wagner M., Cecconi F. 2007. Analysis of Apoptosome Dysregulation in Pancreatic Cancer and of its Role in Chemoresistance. Cancer Biology & Therapy 6, 209-217.

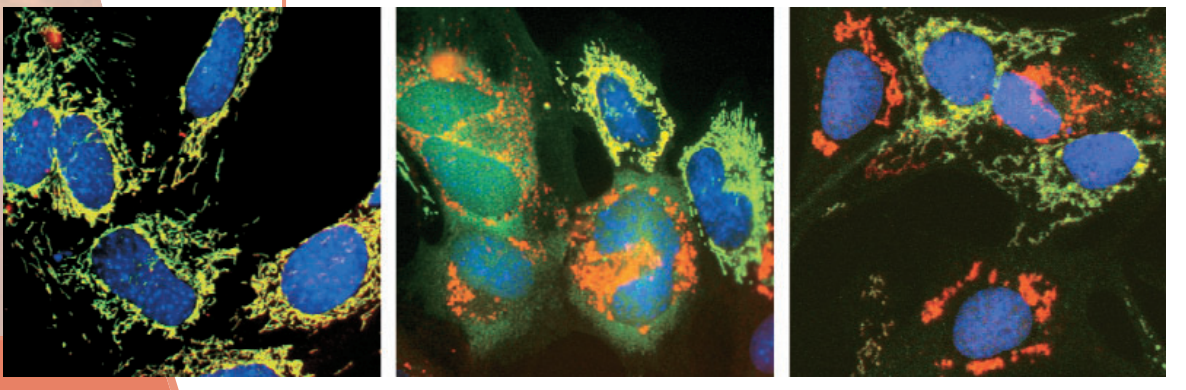
Cozzolino M., Ferri A., Ferraro E., Rotilio G., Cecconi F. and Carri M.T. 2006. Apaf1 mediates apoptosis and mitochondrial damage induced by mutant human SOD1s typical of familial amyotrophic lateral sclerosis. Neurobiology of Disease 21, 69-79.

De Zio D., Giunta L., Corvaro M., Ferraro E. and Cecconi F. 2005. Expanding roles of programmed cell death in mammalian neurodevelopment. Seminars in Cell & Developmental Biology 16, 281-294.

Di Sano F., Ferraro E., Tufi R., Achsel T., Piacentini M. and Cecconi F. 2006. Endoplasmic reticulum stress induces apoptosis by an apoptosome-dependent but caspase 12-independent mechanism. The Journal of Biological Chemistry 281, 2693-2700.

Zermati Y., Mouhamad S., Stergiou L., Besse B., Galluzzi L., Boehrer S., Pauleau A.-L., Rosselli F., D'Amelio M., Amendola R., Castedo M., Hengartner M., Soria J.-C., Cecconi F. and Kroemer G. 2007. Non-apoptotic role for Apaf-1 in the DNA damage checkpoint Molecular Cell 28, 624-637.

Programmed cell death is an orchestrated form of cell death in which cells are actively involved in their own demise. During development in mammals, many progenitor cells, immature cells or differentiated cells undergo the most clearly characterized type of cell death, apoptosis. Several pathways of apoptosis have been linked to embryogenesis, but according to the numerous and striking phenotypes observed when apoptotic genes are inactivated, the mitochondrial pathway is the most important death-route in several tissues during development. The first step of this pathway is the mobilization of BH3 proteins of the Bcl2-like family, which mediate cytochrome release from mitochondria. The release of cytochrome c triggers caspase-9 recruitment on the Apaf1-centered apoptosome. This, in turn, activates caspase-3, a crucial effector of cell destruction.
The apoptosome pathway is also involved in the homeostasis of adult tissues in mammals.
We have performed a molecular and functional characterization of apoptosome components and regulators in a number of physiological and pathological conditions. We have found that a) Endoplasmic reticulum stress induces apoptosis by an apoptosome-dependent but caspase 12-independent mechanism; b) apoptosome dysregulation in pancreatic cancer is prognostic of chemoresistance; c) Apaf1, besides its role in apoptosome regulation, plays a nonapoptotic role in the DNA damage checkpoint. In addition, we have contributed to elucidating what the point-of-no-return in apoptosis is and to clarify the issue of survival of apoptosome-deficient proneural cells under stress conditions. Moreover, we are presently investigating the role played by the apoptosome in the synaptic degeneration that characterizes the onset of Alzheimer's disease.
Unraveling the involvement of the apoptosome components in dysregulated cell death could be highly relevant for pharmacological intervention in oncology and for therapies based on neural stem cell transfer in the treatment of neurological disorders.



The apoptosome machinery triggers cell death upon stress of the endoplasmic reticulum (tunicamycin). After 48 hours of treatment, cytochrome c (green) is released from mitochondria (red, labelled by SOD1 -superoxide dismutase) and activates the apoptosome. Later on, cytochrome c is digested by the proteasome (72 hours) and the green staining disappears from the cells. Cell nuclei are stained in blue (DAPI).

GROUP LEADERS Sergio Filoni • Stefano Cannata ■ **STAFF SCIENTISTS** Sergio Bernardini • Cesare Gargioli

Comparative and experimental morphology: Experimental analysis of regeneration in Amphibians

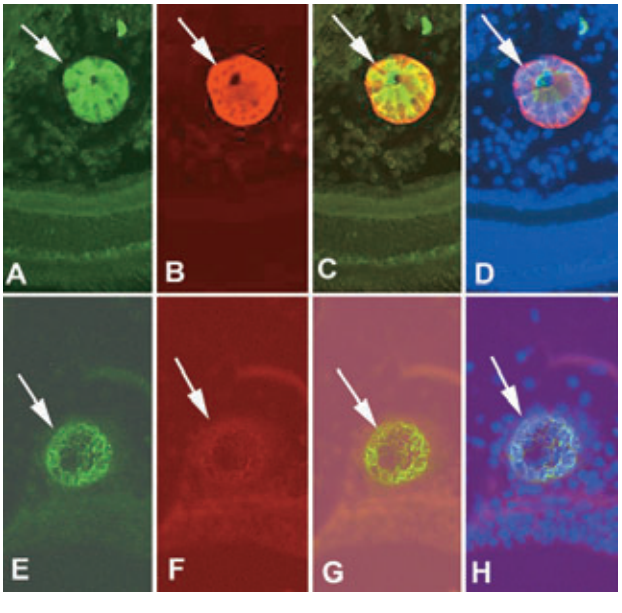
Anuran amphibians have considerable regenerative power in early larval stages, although this potential tends to decrease during larval development and becomes very poor after metamorphosis. The causal analysis of the regenerative processes in Anuran amphibians can provide original contributions for clarifying several questions: Which are the factors involved in the stability of the cellular type and in cellular interactions occurring during regeneration? Are development and regeneration two different processes, or are they directed by the same genes? Which are the causes responsible for the regenerative failure during the evolution of vertebrates? To approach these problems, we use the eye of *Xenopus* larvae as an experimental model. In particular, our studies concern 1) lens regeneration by transdifferentiation of the outer cornea and the regeneration 2) retina regeneration by transdifferentiation of the retinal pigmented epithelium (RPE). Both processes are promoted by inductive factors from the neural retina.

LENS REGENERATION:

Data obtained by Real-time RT-PCR analysis and by classical methods of experimental embryology, demonstrate that the lens-regenerating competence in the outer cornea of *X. laevis* is related to *pax6* expression and corresponds to the persistence of a condition similar to that of the embryonic presumptive lens ectoderm.

The inability of *X. borealis* to regenerate a lens after lentectomy is due to an inhibiting action exerted by the inner cornea on the spreading of a retinal inductive factor from the vitreous chamber towards the outer cornea.

RETINA REGENERATION: Data obtained by in situ hybridization of fragments of retinal pigmented epithelium of *X. laevis* larvae implanted into the vitreous chamber of host eyes indicate that *pax6* has different roles during the RPE to retina transdifferentiation process acting as an early retinal determinant and later directing progenitor cell fate. Moreover, we observed that genes involved in retina development (Xrx1, Xvax2, Xsix3, Xpax6, Xchx10, Xotx2) are actively transcribed in the ciliary marginal zone of the premetamorphic and metamorphic and *X. laevis* larvae.



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Arresta E, Bernardini S., Filoni S., Cannata S.M. 2005. Lens-forming competence in the epidermis of Xenopus laevis during development. Journal of Experimental Zoology, Part A. 303,1548-8969.

Casarosa S., Leone P., Cannata S., Santini F., Pinchera A., Barsacchi G. and Andreazzoli M. 2005. Genetic analysis of metamorphic and premetamorphic Xenopus Ciliary Marginal Zone. Developmental Dynamics, 233,646-651.

GROUP LEADER Lina Ghibelli ■ **PHD STUDENTS** Flavia Radogna • Laura Paternoster

The anti-apoptotic and pro-oxidant effect of melatonin

Radogna F., Paternoster L., Albertini M.C., Cerella C., Accorsi A., Bucchini A., Spadoni G., Diamantini G., Tarzia G., De Nicola M., D'Alessio M., Ghibelli L. 2007. Melatonin antagonizes apoptosis via receptor interaction in U937 monocytic cells. J Pineal Res. 43, 154-162.

Radogna F., Paternoster L., Albertini M.C., Accorsi A., Cerella C., D'Alessio M., De Nicola M., Nuccitelli S., Magrini A., Bergamaschi A., Ghibelli L. 2006. Melatonin as an apoptosis antagonist. Ann N Y Acad Sci. 1090,226-233.

Albertini M.C., Radogna F., Accorsi A., Uguccioni F., Paternoster L., Cerella C., De Nicola M., D'Alessio M., Bergamaschi A., Magrini A., Ghibelli L. 2006. Intracellular pro-oxidant activity of melatonin deprives U937 cells of reduced glutathione without affecting glutathione peroxidase activity. Ann N Y Acad Sci. 1091,10-16.

Among the non-neurological functions of melatonin, much attention is being directed to the ability of melatonin to modulate the immune system, whose cells possess melatonin-specific receptors and biosynthetic enzymes. Melatonin controls cell behavior by eliciting specific signal transduction actions after its interaction with plasma membrane receptors (MT(1), MT(2)); additionally, melatonin potently neutralizes free radicals. Melatonin regulates immune cell loss by antagonizing apoptosis. A major unsolved question is whether this is due to receptor involvement, or to radical scavenging considering that apoptosis is often dependent on oxidative alterations. We have shown that on U937 monocytic cells, apoptosis is antagonized by melatonin by receptor interaction rather than by radical scavenging. First, melatonin and a set of synthetic analogues prevented apoptosis in a manner that is proportional to their affinity for plasma membrane receptors but not to their antioxidant ability. Secondly, melatonin's antiapoptotic effect required key signal transduction events including G protein, phospholipase C and Ca2+ influx and, more important, it is sensitive to the specific melatonin receptor antagonist luzindole.

We have shown that melatonin interferes with the intrinsic pathway of apoptosis at the mitochondrial level. In response to an apoptogenic stimulus, melatonin allows mitochondrial translocation of the pro-apoptotic protein Bax, but it impairs its activation/dimerization The downstream apoptotic events, i.e. cytochrome c release, caspase 9 and 3 activation and nuclear vesiculation are equally impaired, indicating that melatonin interferes with Bax activation within mitochondria. Interestingly, we found that melatonin induces a strong re-localization of Bcl-2, the main Bax antagonist to mitochondria, suggesting that Bax activation may in fact be antagonized by Bcl-2 at the mitochondrial level. Indeed, we inhibit the melatonin anti-apoptotic effect (i) by silencing Bcl-2 with small interfering RNAs, or with small-molecular inhibitors targeted at the BH3 binding pocket in Bcl-2 (i.e. the one interacting with Bax); and (ii) by inhibiting melatonin-induced Bcl-2 mitochondrial re-localization with the MT1/MT2 receptor antagonist luzindole. This evidence provides a mechanism that may explain how melatonin through interaction with the MT1/MT2 receptors, elicits a pathway that interferes with the Bcl-2 family, thus modulating the cell life/death balance.

It was long believed that melatonin might counteract intracellular oxidative stress because it was shown to potentiate antioxidant endogenous defences, and to increase the activity of many antioxidant enzymes. However, it is now becoming evident that when radicals are measured within cells, melatonin increases, rather than decreasing, radical production. Herein we demonstrate a pro-oxidant effect of melatonin in U937 cells by showing an increase of intracellular oxidative species and a depletion of glutathione (GSH). The activity of glutathione peroxidase is not modified by melatonin treatment as it does occur in other experimental models.

GROUP LEADERS Lina Ghibelli ■ **POSTDOCS** Claudia Cerella • Milena De Nicola • Silvia Nuccitelli

Mechanisms of the modulation of apoptosis by magnetic fields

Magnetic fields (MFs) are receiving much attention in basic research due to their emerging ability to alter intracellular signaling. We have show that static MFs with intensity of 6 mT significantly alter the intracellular redox balance of U937 cells. A strong increase of reactive oxygen species (ROS) and a decrease of glutathione (GSH) intracellular levels were found after 2 h of MF exposure and maintained thereafter. We found that also other types of MFs, such as extremely-low-frequency (ELF) MFs affect intracellular GSH starting from a threshold at 0.09 mT. We previously reported that static MFs in the intensity range of 0.3-60 mT reduce apoptosis induced by damaging agents (Fanelli et al., 1998). ELF-MFs are also able to protect U937 from apoptosis. Interestingly, this ability is limited to the ELF intensities able to alter redox equilibrium, indicating a link between MF's antiapoptotic effect and the MF alteration of intracellular redox balance. This suggests that MF-produced redox alterations may be part of the signaling pathway leading to apoptosis antagonism. Thus, we tested whether MFs may still exert an antiapoptotic action in cells where the redox state was artificially altered in both directions, that is, by creating an oxidative (via GSH depletion with BSO) or a reducing (with DTT) cellular environment. In both instances, MFs fail to affect apoptosis. Thus, a correct intracellular redox state is required in order for MFs to exert their antiapoptotic effect.

In another approach, we explored the effect of diagnistic apparatuses of magnetic resonance. NMR technology has dramatically contributed to the revolution of image diagnostic. NMR apparatuses use combinations of microwaves over a homogeneous strong (1 Tesla) static magnetic field. We had previously shown that low intensity (0.3-66 mT) static magnetic fields deeply affect apoptosis in a Ca2+ dependent fashion (Fanelli et al., 1999 FASEBJ., 13;95-102). The rationale of our study was to examine whether exposure to the static magnetic fields of NMR can affect apoptosis induced on reporter tumor cells of haematopoietic origin.

The impressive result was the strong increase (1.8-2.5 fold) of damage-induced apoptosis by NMR. This potentiation is due to cytosolic Ca2+ overload consequent to NMR-promoted Ca2+ influx, since it is prevented by intracellular (BAPTA-AM) and extracellular (EGTA) Ca2+ chelation or by inhibition of plasma membrane L-type Ca2+ channels. Three-days follow up of treated cultures shows that NMR decreases long term cell survival, thus increasing the efficiency of cytocidal treatments. Importantly, mononuclear white blood cells are not sensitised to apoptosis by NMR, showing that NMR may increase the differential cytotoxicity of antitumor drugs on tumor vs normal cells. This strong, differential potentiating effect of NMR on tumor cell apoptosis may have important implications, being in fact a possible adjuvant for antitumor therapies.

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Nuccitelli S., Cerella C., Cordisco S., Albertini M.C., Accorsi A., De Nicola M., D'Alessio M., Radogna F., Magrini A., Bergamaschi A., Ghibelli L. 2006. Hyperpolarization of plasma membrane of tumor cells sensitive to antiapoptotic effects of magnetic fields. Ann N Y Acad Sci. 1090,217-225.

GROUP LEADER Lina Ghibelli ■ **POSTDOC** Claudia Cerella

Role of Ca^{2+} as a regulator of apoptosis

Cerella C., Mearelli C., Coppola S., D'Alessio M., De Nicola M., Diederich M., Ghibelli L. Sequential phases of Ca2+ alterations in pre-apoptotic cells. (2007) Apoptosis. 12,2207-2219.

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Cerella C., Mearelli C., Ammendola S., De Nicola M., D'Alessio M., Magrini A., Bergamaschi A., Ghibelli L. 2006. Molecular determinants involved in the increase of damage-induced apoptosis and delay of secondary necrosis due to inhibition of mono(ADP-ribosyl)ation. Ann N Y Acad Sci. 1090,50-58.

Many studies suggest that endoplasmic reticulum (ER) Ca2+ pool rather than cytosolic Ca2+ may play a crucial role in triggering apoptosis. We performed an image analysis of cells loaded with the fluorescent dye chlortetracycline (CTC) to in situ analyze Ca2+ changes within the ER in apoptosing promonocytic U937 cells. The results, validated through the use of thapsigargin (THG) as ER Ca2+ depletor, confirm the findings that apoptotic cells have a Ca2+-depleted ER, in contrast with treated but still viable cells.

The very early events of the intrinsic, damage-induced apoptotic pathway, i.e., upstream to Bax activation, probably consist of physico-chemical alterations (i.e., redox, pH or Ca2+ changes) rather then subtle molecular interactions, and in spite of many studies they remain unclear. One problem is that cells undergo apoptosis in an asynchronous way, leading to heterogeneity in the cell population that impairs the results of bulk analyses. In this study, we present a flow cytometric approach for studying Ca2+ alteration in apoptosis at the single cell level.

By means of a multiparametric analysis, we were able to discriminate different sub-populations, i.e., viable and apoptotic cells and cells in secondary necrosis, and separately analyse static as well as dynamic Ca2+ parameters in each sub-population. With this approach, we have identified a set of sequential Ca2+ changes; two very early ones occur prior to any other apoptotic alterations, whereas a later change coincides with the appearance of apoptosis. Interestingly, the two pre-apoptotic changes occur simultaneously in all treated cells, i.e., at fixed times post-treatment, whereas the later one occurs at varying times, i.e., within a wide time range, concomitantly with the other apoptotic events.

Thapsigargin (THG), a selective inhibitor of endoplasmic reticulum (ER) Ca2+-ATPases, causes the rapid emptying of ER Ca2+; in some cell types, this is accompanied by apoptosis, whereas other cells maintain viability. In order to understand the molecular determinants of such a different behavior, we explored the role of oxygen versus nitrogen radicals, by analyzing the apoptogenic ability of THG in the presence of inhibitors of glutathione or nitric oxide (NO) synthesis, respectively. We observed that oxygen radicals play a sensitizing role whereas nitrogen radicals prevent THG-dependent apoptosis, showing that the apoptogenic effect of THG is redox sensitive.

Tumor cells often develop molecular strategies for survival to anoxia/reoxygenation stress as part of tumor progression. Here we describe that the B lymphoma Epstein-Barr-positive cells E2r survive reoxygenation in spite of a very high and long-lasting increase in cytosolic Ca2+ and the loss of about half of their mitochondria due to specific extrusion of the organelles from the cells. The extrusion typically occurs 3 days after reoxygenation, and a regular mitochondrial asset is regained after a further 24 h.

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Redox modulation of apoptosis and survival: the role of the Bcl-2 family proteins

In many cell systems, pharmacological glutathione (GSH) depletion with the GSH neosynthesis inhibitor buthionine sulfoximine (BSO) leads to cell death and highly sensitizes tumor cells to apoptosis induced by standard chemotherapeutic agents. However, some tumor cells upregulate Bcl-2 in response to BSO, thus surviving the treatment and failing to be chemosensitized. Cell lines of monocytic and lymphocytic origins respond to BSO treatment in an opposite way, lymphocytes being chemosensitized and unable to transactivate Bcl-2. In lymphocytes freshly isolated from peripheral blood of healthy donors BSO promotes the upregulation of Bcl-2, with a mechanism involving the increased radical production consequent to GSH depletion. Thus, BSO treatment may increase the differential cytocidal effect of cytotoxic drugs in tumor versus normal lymphocytes.

Bax is a cytosolic protein, which in response to stressing apoptotic stimuli, is activated and translocates to mitochondria, thus initiating the intrinsic apoptotic pathway. In spite of many studies and the importance of the issue, the molecular mechanisms that trigger Bax translocation are still obscure. We show by computer simulation that the two cysteine residues of Bax may form disulfide bridges, producing conformational changes that favor Bax translocation. Oxidative, non-apoptogenic treatments produce an up-shift of Bax migration compatible with homo-dimerization, which is reverted by reducing agents; this is accompanied by translocation to mitochondria. Dimers also appear in pure cytosolic fractions of cell lysates treated with H_2O_2, showing that Bax dimerization may take place in the cytosol. Bax dimer-enriched lysates support Bax translocation to isolated mitochondria much more efficiently than untreated lysates do, indicating that dimerization may promote Bax translocation. The absence of apoptosis in our system make it possible to demonstrate that Bax moves because of oxidations, even in the absence of apoptosis. This provides the first evidence that Bax dimerization and translocation respond to oxidative stimuli, suggesting a novel role for Bax as a sensor of redox imbalance.

U937 monocytic cells show two main apoptotic nuclear morphologies, budding and cleavage, that are the result of two independent morphological routes, since they never interconvert one into the other, and are differently modulated by stressing or physiological apoptogenic agents [Exp Cell Res 1996; 223:340-347]. With the aim of understanding which biochemical alterations are at the basis of these alternative apoptotic morphologies, we performed an in situ analysis that showed that in U937 cells intracellular glutathione (GSH) is lost in cells undergoing apoptosis by cleavage, whereas it is maintained in apoptotic budding cells. Lymphoma cells BL41 lose GSH in apoptosis, and show the cleavage nuclear morphology; the same cells latently infected with Epstein Barr Virus (E2r line) undergo apoptosis without GSH depletion and show the budding nuclear morphology. GSH depletion is not only concomitant to, but is the determinant of the cleavage route.

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Role of type 2 Transglutaminase in physiology and pathology

Battaglia G., Farrace M.G., Mastroberardino P.G., Viti I., Fimia G.M., Van Beeumen J., Devreese B., Melino G., Molinaro G., Busceti C.L., Biagioni F., Nicoletti F., Piacentini M. 2007. Transglutaminase 2 ablation leads to defective function of mitochondrial respiratory complex I affecting neuronal vulnerability in experimental models of extrapyramidal disorders. J Neurochem., 36-49.

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Tissue or type 2 Transglutaminase (TG2) is a special member of the large transglutaminase family, characterised by its ability to form Ca^{2+} dependent intra- and/or inter-protein cross-links. In addition, TG2 has been described as able to function as a G-protein, as a kinase and, very recently, as a Protein Disulphide Isomerase (PDI). These multiple activities involves the enzyme in a multitude of cellular process, from cell death to signalling, but its real physiological role remain quite obscure.

We have previously reported that $TG2^{-/-}$ mice showed a defective clearance of apoptotic cells associated with the development of splenomegaly, autoantibodies, and glomerulonephritis. The lack of TG2 results in an impaired capacity of macrophages to engulf, but not to bind, apoptotic cells, which is paralleled by an abnormal inflammatory response both in vivo and in vitro. We found that the expression of both TGF-beta and IL-12 was significantly altered in the absence of TG2. These results help explain the autoimmune phenotype developed by these mice and suggest that TG2 is a key regulatory element of the anti-inflammatory features of apoptosis.

In addition, we investigated the role of TG2 in respect to the mitochondrial physiology. The analysis of $TG2^{-/-}$ mice provided the first in vivo evidence showing that, under physiological conditions, TG2 might act as a Protein Disulphide Isomerase (PDI) and that through this activity it contributes to the correct assembly of the respiratory chain complexes. We observed a reduction in the complex I activity, partially complemented by an increase in the complex II activity.

The molecular basis of this phenotype relies on a defective disulphide bond formation in ATP synthase (complex V), NADH-ubiquinone oxidoreductase (complex I), succinate-ubiquinone oxidoreductase (complex II) and cytochrome c oxidase (complex IV). This impairment results in a reduced ATP production, not evident under restful conditions but that become clear under stressful conditions. In addition, $TG2^{-/-}$ mice turn out to be protected against nigro-striatal damage induced by the mitochondrial complex I inhibitor MPTP/MPP^+ and more vulnerable to the damage induced by methamphetamine or by the complex II inhibitor, 3-NP. Proteomic analysis showed that proteins involved in the mitochondrial respiratory chain, such as prohibitin and the beta-chain of ATP synthase, are substrates for TG2. Taken together, these results suggest that TG2 is involved in the regulation of the respiratory chain both in physiology and pathology, contributing to set the threshold for neuronal damage in Huntington's disease and other extra-pyramidal disorders.

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Molecular components of ER stress-induced apoptosis: new targets for alternative cancer therapeutic strategies

Early induction of apoptosis of tumour cells is the preferred treatment option of human cancer. To identify factors that specifically induce apoptosis in cancer cells but not in normal tissue is one of the major goals for cancer therapy. Studies from many laboratories point to the endoplasmic reticulum (ER) as a novel subcellular compartment implicated in apoptotic execution.

It has been reported that alteration in Ca^{2+} homeostasis and accumulation of unfolded proteins in the endoplasmic reticulum lead to an ER stress response which may induce cell death; nevertheless the signalling pathways that emerge from this organelle remain largely obscure.

Our group for many years has been interested in the characterization of the molecular components of apoptotic signaling pathway. In last few years we have focused on alternative cell death pathways, particularly ER-stress-related ones.

We have shown that ER stress-induced apoptosis of mouse neuronal cells occurs via an Apaf-dependent cell death pathway and does not require the cleavage of the ER resident caspase-12.

We have also been interested in elucidating the role of the reticulon family member RTN-1C in the mechanism of apoptosis induction. Reticulons are a new family of proteins, primarily localized on the ER membrane, which have attracted particular interest due to their implication in cellular processes such as apoptosis or axonal regeneration.

We demonstrate that RTN-1C is able to modulate in a mutually exclusive way the cellular sensitivity to different apoptosis pathways. In fact the increase of RTN-1C protein levels per se results in ER-stress induced cell death, mediated by an increase of cytosolic Ca^{2+}, and significantly sensitizes cells to different ER stress inducers. In line with these findings the reduction of RTN-1C, by antisense DNA expression, abrogates the responce to ER-stressors. In the presence of high RTN-1C levels, genotoxic drugs become ineffective as a consequence of the cytoplasm translocation of p53 protein, while the silencing of endogenous RTN-1C results in the potentiation of the genotoxic drugs action. Moreover we found that RTN-1C overexpression is directly correlated to CRT exposure on the plasma membrana, through a mechanism mediated by the reduction of ER Ca^{2+}, which has been demonstrated as important for the activation of anti-cancer immune response and cell death. In fact the exposure of CTR has been correlated to immunogenic cell death after anthracycline and g-radiation in mouse models. Thus it is both necessary and sufficient to render conventional chemotherapies immunogenic.

The comprehension of how an alteration of the ER compartment can be translated into an apoptotic response would be of great importance to the design of new therapeutic approaches for cancer therapy which can act alone or in combination with the p53-dependent apoptosis pathway.

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Myosin V and Rab/Ypt proteins in vesicle trafficking and disease

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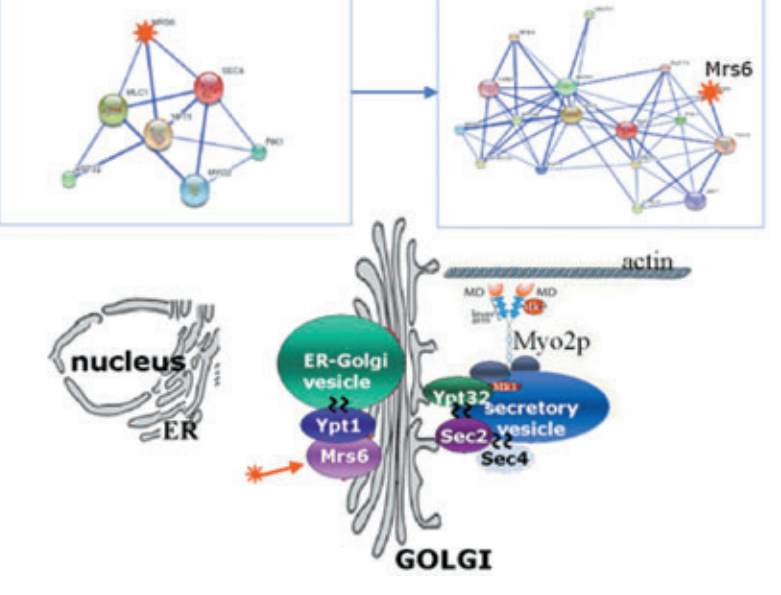
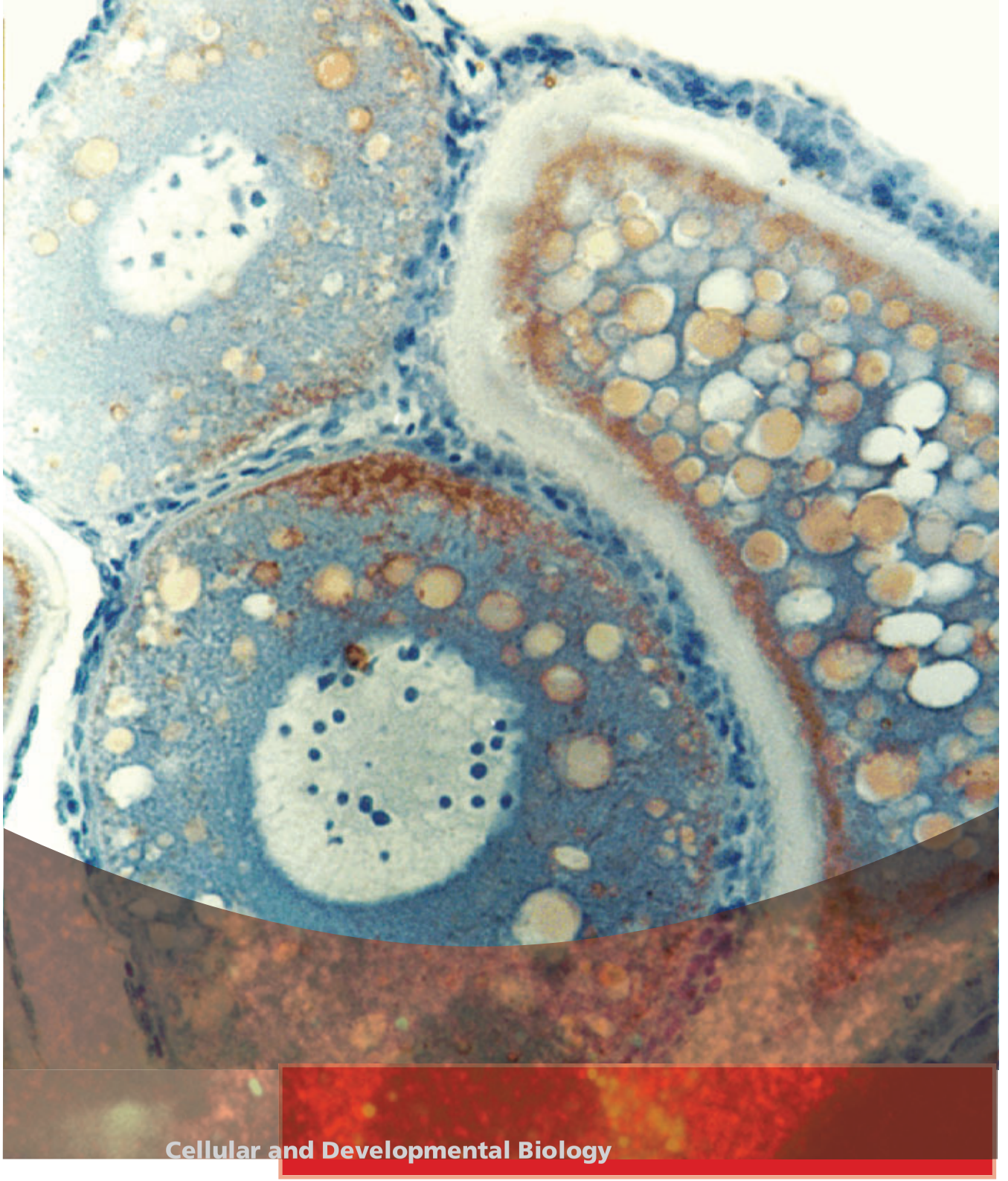
An increasing number of human dysfunctions are being found to be due to defects in intracellular membrane trafficking. Defects in Myosin V and Rab/Ypt small GTPase-mediated transport of carriers appear to affect in particular skin pigmentation, immunological responses and neuronal function. The nervous system appears to be extremely sensitive to defects in Myosin V (MyoV) function. The structural and functional conservation between yeast and humans of the molecular machinery required for anchoring and movement of intracellular membranes along the secretory pathway has allowed the use of the budding yeast *Saccharomyces cerevisiae* for the characterization of the basic components of this machinery (1).

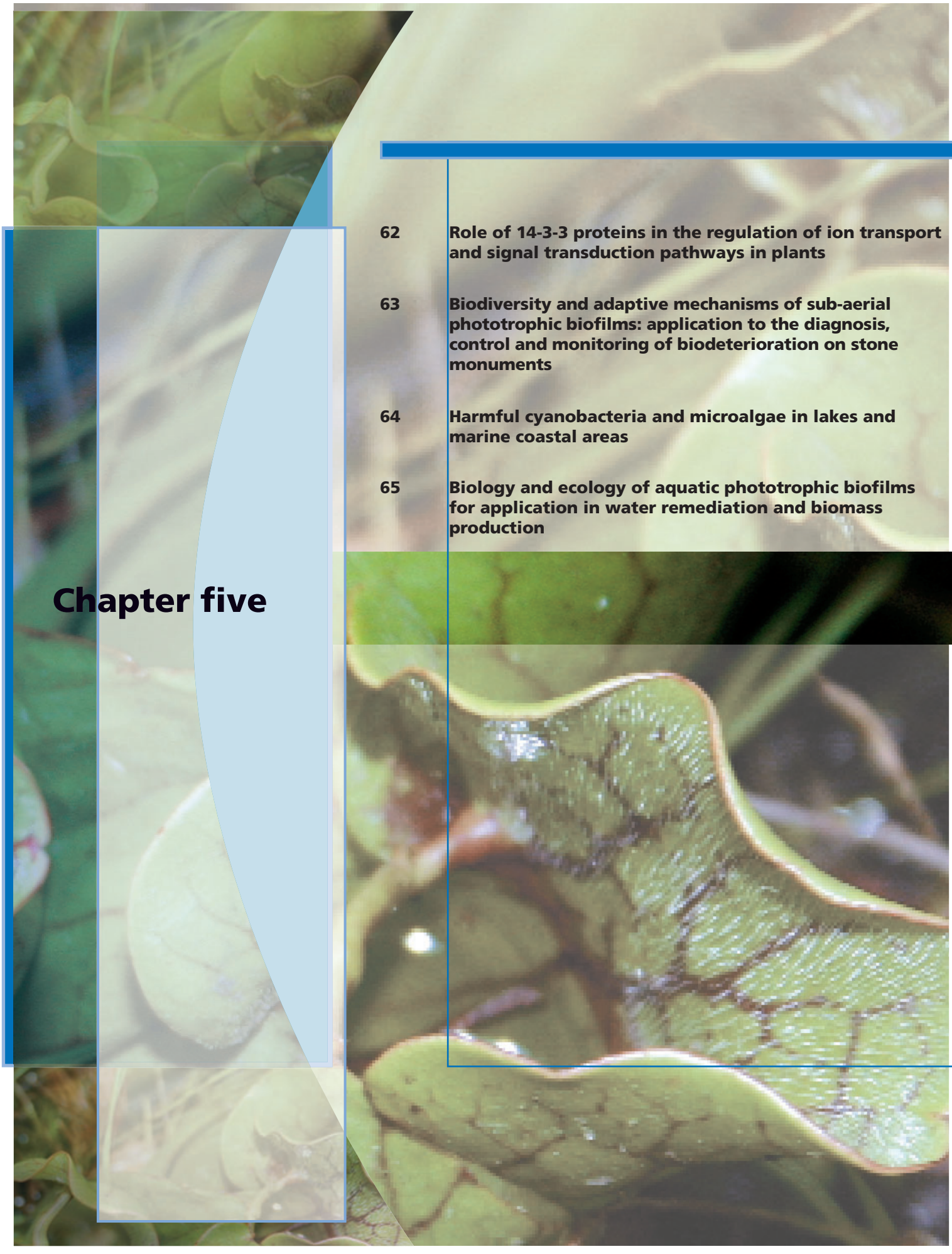
For several years my laboratory has focused on the characterization of the protein network regulating the anchoring and movement of secretory vesicles from the ER to the plasma membrane using budding yeast as a model system (1).

We first identified the yeast Rab Escort Protein, Mrs6 (red asterisk in the Figure), as an essential yeast gene required for Rab/Ypt prenylation. Mrs6p is a homologue of the human CHM/REP1. Defects in REP1 cause an X-linked retinal dystrophy named Choroideremia (CHM). To characterise the function of REP/Mrs6 we used conditional-lethal mutants, genetic screens, and biochemical and cell biology tools. Lowering Mrs6p activity, and thus Rab/Ypt protein prenylation, causes defects primarily in the trafficking of membranes from the TGN to the plasma membrane. This trafficking step requires the Sec4 and Ypt31/32 Rab/Ypt proteins that, we have shown, act as linkers between the yeast myosin V Myo2p and secretory vesicle membranes (1-3). Furthermore, we have identified the essential myosin light chain 1 (Mlc1p) in complexes with Myo2p, Sec4p and Ypt32p and have shown that Mlc1p acts in cytokinesis as a regulator of vesicle delivery during actomyosin ring contraction (1-5). Our structural analysis of Myo2p/Mlc1p complex(es) (4,5) allowed us to identify a possible Mlc1p human homologue. Our current aim is to further characterise the components of secretory machinery using High Content Screening Microscopy technologies applied to mammalian cell-based assays. These types of studies are expected to provide new avenues for the development of therapeutic approaches for human inherited dysfunctions based on defects in the secretory pathway.





Cellular and Developmental Biology



Chapter five

Plant Biology

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Role of 14-3-3 proteins in the regulation of ion transport and signal transduction pathways in plants

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The 14-3-3 proteins are a family of conserved regulatory molecules expressed in all eukaryotic cells. A striking feature of the 14-3-3 proteins is their ability to bind a multitude of functionally diverse signalling proteins in a phosphorylation-dependent manner. This plethora of interacting proteins allows 14-3-3s to play important roles in a wide range of vital regulatory processes, such as mitogenic signal transduction, apoptotic cell death, and cell cycle control.
A number of peculiar functions have been assigned to 14-3-3 proteins in plants, such as regulation of primary metabolism, ion transport and cellular trafficking. The research activity of our laboratory is mainly focused on the study of 14-3-3 proteins' role in ion transport. In particular, we have been investigating the role of 14-3-3 proteins in the regulation of the plasma membrane H^+-ATPase.
We identified physiological signals, such as polyamines and sugars, able to activate the proton pump by stimulating the association of 14-3-3 proteins. Furthermore, the H^+-ATPase/14-3-3 association was dissected at the molecular level to identify amino acids and domains involved in the interaction. We identified an unusual (type III) 14-3-3 binding domain on the H^+-ATPase and a novel interaction mechanism involving the C terminal domain of 14-3-3 proteins.
We recently demonstrated the ability of 14-3-3 proteins to bind and activate the Arabidopsis K^+ channel KAT1. Since the activity of KAT1 is strictly dependent on the membrane hyperpolarization created by the H^+-ATPase, this finding points to a role for 14-3-3 proteins as general regulators of ion transport across the plasma membrane.
We also demonstrated the ability of 14-3-3 proteins to bind to a maize MAP kinase (Mitogen-activated protein kinase) Since MAPKs are important signal transducing enzymes that connects diverse receptors/sensors to a wide range of cellular responses, our finding potentially expands the range of 14-3-3 functions in plants.
In order to assign novel functions to 14-3-3 proteins, transgenic plants with altered 14-3-3 levels have also been produced. The physiological and biochemical analysis of these plants and the study of the response to biotic and abiotic stresses are currently in progress. Possible biotechnological applications of this plants are also under investigation.

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In collaboration with: D. Billi, this department; G. Palleschi and G. Paradossi, Dept. Chemical Sciences and Technology of this University; R. De Philippis, University of Florence; G. Zammit, Heritage Malta; S.P. Adhikary, Utkal University, India

Biodiversity and adaptive mechanisms of sub-aerial phototrophic biofilms: application to the diagnosis, control and monitoring of biodeterioration on stone monuments

Sub-aerial microbial phototrophic communities develop as "biofilms" on exposed lithic faces in a wide range of environments and climatic zones on soils, rocks as well as on monuments. Biofilm settlement and persistence on exposed stones in archeological sites of sub-tropical and tropical regions relays on microbial capability to face abiotic and biotic stresses. Epilithic biofilms consist of consortia of poikilo-tolerant microorganisms representative of phylogenetically distant taxa, including bacteria, cyanobacteria, algae, fungi and lichens. Among them, phototrophic organisms are a key component since they provide the consortium with organic substrates and oxygen.

The research focuses on the investigation of different typologies of epilithic phototrophic biofilms, that develop either outdoors under high solar radiation and reduced water availability or indoors, in very humid and scarcely illuminated archaeological sites, in Italy, Malta and India. Cyanobacteria and their relationships with the associated microorganisms and with the colonised surfaces are characterised, and the exopolymeric substances (EPS), that play a basic role in the adhesion and cohesion of the microbial community and in the mobilisation of stone element are analysed. Biofilm fragments are removed from the underlying valuable substrata using non-invasive sampling techniques. Their architecture and diversity is studied using microscopy (LM, LFM, CLSM, SEM; EFTEM-ESI) and molecular methods (DNA fingerprinting, 16S rRNA gene and ITS sequencing), and cultures are established to assess and compare the ecophysiological response (photosynthesis, light acclimation) and morpho-functional changes (EPS structure and composition) of the whole community and isolates under varied experimental conditions.

In parallel, the research aims to further develop innovative and non-invasive methods started within the EU Project CATS (EVK4-CT2000-00028) for the diagnosis and prevention of the growth of phototrophic biofilms on artefacts as well as to establish monitoring protocols able to detect and quantify biofilm development. Control methods include the testing of molecules able to interfere with the adhesion mechanisms to prevent the development of biofilm, the use of monochromatic lamps inside confined environments to reduce the growth of phototrophs, and the use of PAM fluorimetry and portable spectroradiometry to verify and/or monitor the efficacy of the newly developed control and eradication procedures.

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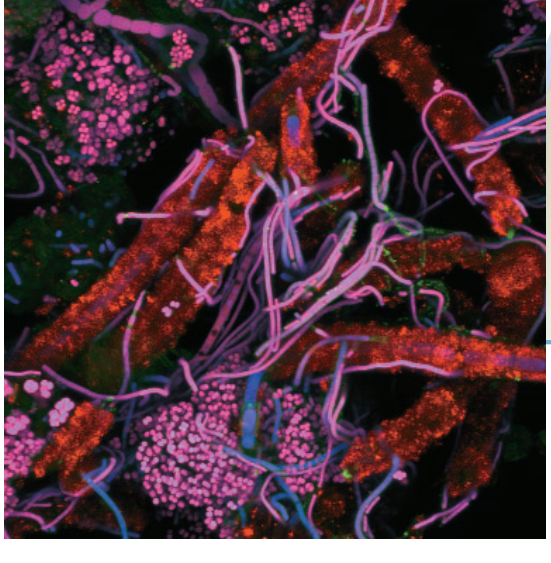

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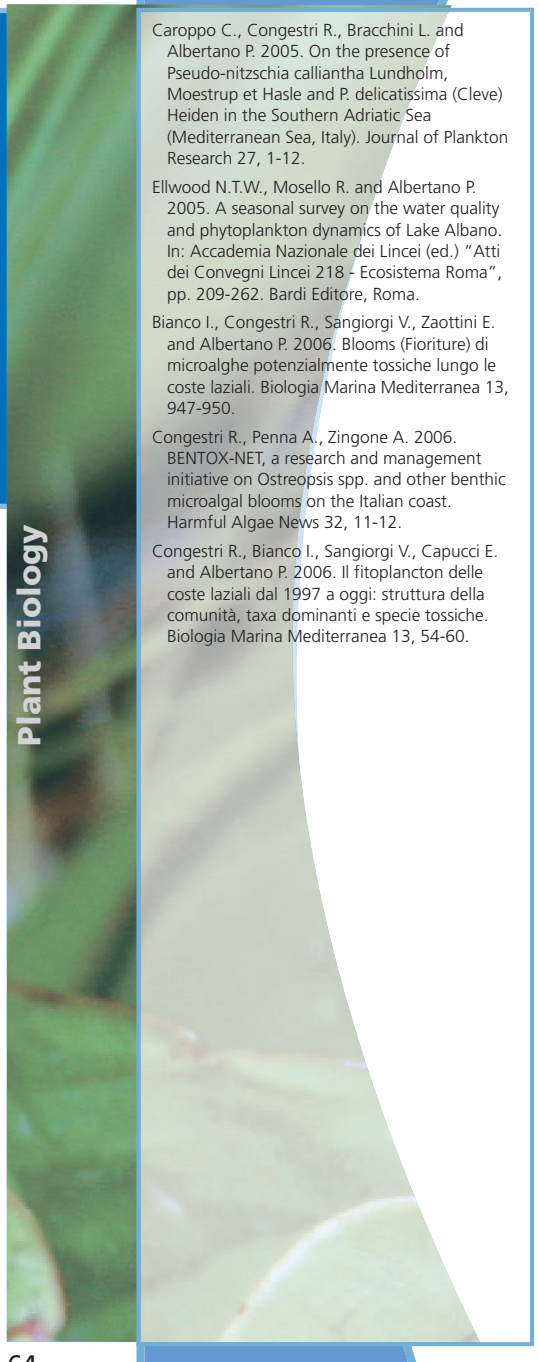
Harmful cyanobacteria and microalgae in lakes and marine coastal areas



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Several phytoplanktic cyanobacteria and microalgae are responsible for extensive blooms in natural and artificial basins in Italy. Studies are conducted on the characterisation of harmful species, particularly on those able to produce toxins in Lake Albano in Latium (Italy), also with the aim of developing useful monitoring approaches. Many different cyanobacteria naturally produce toxins that in sufficient quantities can cause death of animals and pose a risk to human health. The types of toxin mainly fall into two categories, hepatotoxins and neurotoxins. These toxins are usually released into water when algae form surface blooms/scums and the cells rupture or die.
The research aims to identify the cause of these blooms as a first step in the creation of a management strategy to reduce, control or avoid the associated problems. Within the scope of the present study is the evaluation of the physical, chemical and biological factors that initiate, maintain and terminate the bloom and toxin production. The seasonal succession of the diverse cyanobacterial populations are followed at regular intervals and more intensively during bloom. This work also involves tracing morphological and physiological variations, molecular phylogeny and protein characterisation of the representative cyanobacterial species.

Coastal waters of the Latium region with high recreational and aquaculture value are severely impacted by harmful algal blooms (HABs) mostly due to the development of toxic phytoplanktic dinoflagellates and diatoms. Research aims to increase knowledge on the biology and ecology of major bloom-forming taxa, and to apply novel electrochemical immunosensors able to detect phycotoxins and trace their fate along the trophic chain with the final goal of developing a fast, inexpensive but effective tool for early warning and prevention of water and seafood contamination. In addition, the recent problem posed by the high toxicity of Harmful Benthic Algal Blooms (HBABs) has given rise to studies focused on the analysis of causes and mechanisms that support the development of *Ostreopsis* species along Italian coasts, a novel potential danger for human health and the marine ecosystem.

GROUP LEADER Patrizia B. Albertano • **STAFF SCIENTIST** Roberta Congestri ■ **POST-DOC** Antonella Guzzon ■ **PHD STUDENT** Francesca Di Pippo ■ **COLLABORATORS** G. Paradossi, Dept. Chemical Sciences and Technology of this University; R. De Philippis, University of Florence; E.J. Cox, and E. Shubert, Natural History Museum of London; A. Bohn, New University of Lisboa

Biology and ecology of aquatic phototrophic biofilms for application in water remediation and biomass production

The project aims to study aquatic phototrophic biofilms that develop in freshwater and marine environment in order to produce a model that describes the structure, species composition and dynamics, and physiological processes of biofilms.
At present, research is focusing on phototrophic communities that develop in wastewater treatment plants, the aim being to characterize the structure and the ecophysiology of the microbial consortia, to identify component phototrophic species, and to evaluate the ability of individual taxa to remove nutrients and toxicants still present in the effluents. Growth (biomass) and development of biofilm samples, periodically collected from the walls of secondary treatment tanks and cultured in prototype incubators appositely developed in the frame of the EU project PHOBIA (QLK3-CT2002-01938*),* are analysed using a variety of microscopy, chemical and biochemical techniques. The positioning of dominant biofilm-producing organisms, mainly cyanobacteria and diatoms, is detected by laser scanning microscopy in combination with fluorescent dyes, and this information is included in the analysis and quantification of structure. Major physiological processes are quantified: photosynthesis and respiration, production and composition of exocellular polymeric substances (EPS), along with the capability of removing nitrogen and phosphorus from the water in order to characterise the metabolic activity of the biofilms at different developmental stages.
The information produced by the different data sets is being used to develop a unifying conceptual model, based on artificial neural networks (ANN) that is essential for management and control of aquatic phototrophic biofilms in various existing and new applications, i.e. effects of antifoulants and bioremediation of waters. Furthermore, isolation of phototrophs in culture is being carried out to select strains potentially useful in tertiary treatments and biomass production.

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GROUP LEADER Daniela Billi ■ **COLLABORATORS** C.S. Cockell (Open University, Milton Keynes, UK), S. Onofri (Università della Tuscia, Viterbo, Italy) and P. Ghelardini (IBPM-*CNR*, Roma, Italy)

Survival strategies in desert cyanobacteria: from anhydrobiosis to astrobiology

Cockell C., Schuerger A., Billi D., Friedmann E.I., and Panitz C. 2005. Effects of a simulated martian UV flux on the cyanobacterium Chroococcidiopsis sp. 029. Astrobiology. 5,127-140.

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Research aims to understand how desert cyanobacteria belonging to the genus *Chroococcidiopsis* can withstand the physiological constraints imposed by the complete removal of water, prolonged storage in the air-dry state and subsequent rewetting. Even though water and life are inseparable, a small but diverse group of organisms, which includes animals, plants and microbes, can dry without dying, a phenomenon known as anhydrobiosis (life without water). Anhydrobiotic cells of *Chroococcidiopsis* thrive at the physical limit of life in extremely arid habitats on Earth, such as the McMurdo Dry Valleys (Antarctica) and the Atacama desert (Chile), which are considered the closest terrestrial analogs of Mars. In its natural environment, to escape the harsh outside climate *Chroococcidiopsis* occupies the last refuges for life inside porous rocks or at the stone-soil interfaces, where it survives in a dry, ametabolic state for prolonged periods

Because of their lifestyle and capability to cope with environmental extremes which exceed those they ever encounter in nature, such as ionizing radiation doses as high as 15 KGy, desert strains of *Chroococcidiopsis* are currently used as phototrophic models for exobiological studies dealing with litho-panspermia, search for life beyond Earth, habitability of Mars and planetary protection. Ground-based simulations and low Earth orbit experiments proved that this rock-inhabitant cyanobacterium: 1) withstands for a few minutes exposure of a simulated Martian UV flux (a 10 times higher survival than that reported for spores of *Bacillus subtilis*), ii) dies following atmospheric entry after having orbited the Earth for 16 days; and iii) survives to simulated shock pressures up to 10 GPa (the launch window of Martian meteorites is from 5–10, to 50–55 GPa).

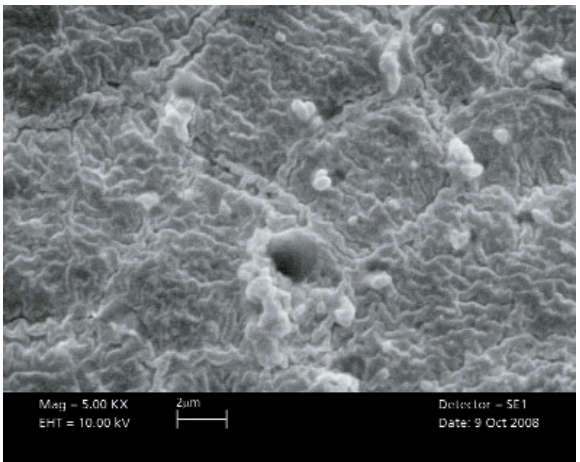
Since genomic stability is affected by exposure to space and Martian radiation as well as to desiccation and ionizing radiation, ongoing researchers aim to unravel the interplay between DNA repair and protection mechanisms in *Chroococcidiopsis*. Indeed experimental evidence suggests that the survival of this cyanobacterium in terrestrial and extraterrestrial DNA damaging conditions relies on its capability to either avoid (limit) DNA damage and repair it upon rehydration. Researches take advantage of molecular tools recently developed for this cyanobacterium, ranging from gene transfer technologies, gene inactivation, shuttle plasmids and GFP-tagging systems. Even though major limitations in identifying DNA repair genes are due to the lack of the genome sequence of *Chroococcidiopsis*, results have been achieved in identifying proper baits for DNA repair proteins and cloning of DNA repair gene fragments.

Researches are funded by the Italian Space Agency (MoMa project)

GROUP LEADER Antonella Canini ■ **PHD STUDENTS** Daniela Alesiani • Lorena Canuti • Elena Pichichero
■ **TECHNICAL ASSISTANTS** Donatella Leonardi

Natural compounds from medicinal plants

Phytochemical analysis and biological screenings of vegetable extracts from *Sida acuta* and *Malva sylvestris* leaves, *Castanea sativa* and *Eucalyptus camaldulensis* pollen were carried out. Chemical analyses were focused on secondary metabolites, particularly phenolic compounds, which have several roles in the plant physiological processes and demonstrated significant capacity in the prevention and care of human health diseases. Solid phase extraction (SPE) and analyses with liquid chromatography and mass spectrometry (HPLC-MS) allowed the identification of 5,7-dimethoxycoumarin, kaempferol, quercetin, genistein, apigenin and myricetin. Moreover, the *M. sylvestris* and *S. acuta* extracts demonstrated a cytotoxic activity on murine and human cancer cell lines, B16 and A375 respectively, by using a MTT assay.
Moreover, we investigated the antimicrobial activity of alkaloids from *S. acuta*. The compounds demonstrated a good activity against the tested microorganisms. In the agar-well diffusion assay, highest inhibition zone diameters were recorded with Gram-positive bacteria. The broth microdilution assay gave minimal inhibitory concentration values ranging from 16 to 400 µg/ml and minimal bactericidal concentration values ranging from 80 to up to 400 µg/ml. The gas chromatography-mass spectrometry analysis (GC-MS) of the same alkaloids led to the identification of cryptolepine and quindoline as the major components.
Finally, our investigation in medicinal plants subject was focused in chemical composition of *Carica papaya* (papaya) extract. The plant is used in tropical diets as a fruit or vegetable; it is also employed as therapeutic remedy for several diseases. Extract was obtained using aqueous methanol in a Soxhlet apparatus and analyzed with gas chromatography-mass spectrometry (GC–MS) in the selected ion-monitoring (SIM) mode. 5,7-Dimethoxycoumarin and polar molecules such as protocatechuic acid, p-coumaric acid, caffeic acid, chlorogenic acid, kaempferol and quercetin were detected and identified in qualitative analysis.
The quantitative analysis showed the presence of phenolic acids as the main compound, while chlorogenic acid was found in trace amounts, compared to the flavonoids and coumarin compounds.
In cellular and molecular fields, we are analyzing the antiproliferative activity of 5,7-dimethoxycoumarin on murine (B16) and human (A375) melanoma cell lines. We selected this secondary metabolite because there is not much data in literature about its biological activity in animal cells. The compound significantly reduced cell proliferation blocking cell cycle in G_0/G_1 phase both in B16 and A375 cells. Moreover, a differentiation process following this block was detected by monitoring some specific markers such as morphological changes with development of dendrite-like projections from cell surface, melanin synthesis and protoporphyrine IX accumulation. In molecular studies, we observed a reduction in expression of phosphorylated form of ERK 1/2 (extracellular signal-regulated kinase), a member of the Ras/Raf/Mek/ERK mitogen-activated protein kinase (MAPK) signalling pathway that is constitutively activated following mutations in 70% of melanomas.



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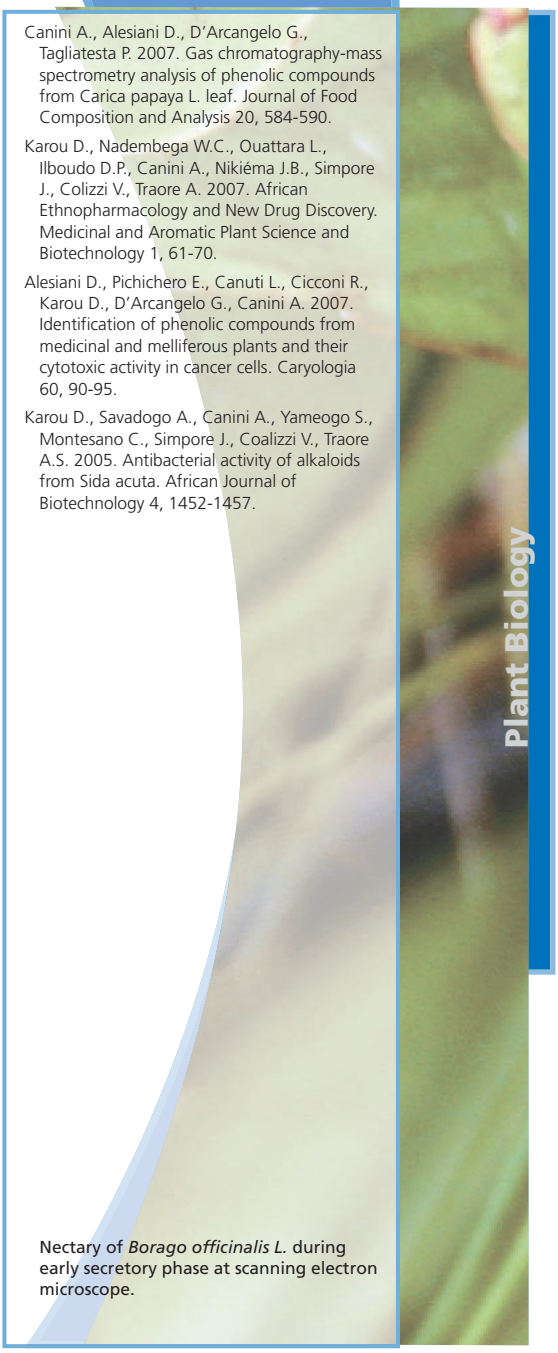

Nectary of *Borago officinalis L.* during early secretory phase at scanning electron microscope.

GROUP LEADER Cinzia Forni ■ **STAFF SCIENTIST** Luciana Migliore ■ **PHD STUDENTS** Barbara Conte • Roberto Braglia

Aquatic plants and the phytoremediation of pollutants

Conte B., Basile A., Castaldo Cobianchi R. e Forni C. 2005. Determinazione dell'attività enzimatica della fenilalanina ammoniaca liasi (PAL) in Lemna minor L. trattata con metalli pesanti. Informatore Botanico Italiano 37 (1 parte B), 634-635.

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Conte B., Braglia R., Basile A., Castaldo Cobianchi R. and Forni C. 2007. Proteomic and Bryophyte: comparison of different methods of protein extraction to study protein synthesis in the aquatic moss Leptodictyum riparium (Hedw.). Caryologia 60, 102-105.

Phytoremediation is the name given to a set of technologies that use plants to clean contaminated sites, such as soils, sediments, and water. It is applicable at sites containing organic, nutrient, or metal pollutants that can be accessed by the roots of plants and sequestered, degraded, immobilized, or metabolized in place. Research efforts into remediation of the pollutants can be roughly categorized into two sets: exploration of the mechanisms and evaluation of claims. Mechanism work has centered on finding theoretical limits, and explanations for the observed alterations in plant behaviour. Pilot-scale field work has both preceded and followed explanatory laboratory research, and early successes have roused interest. Long-term, objective field evaluation is critical to understanding how well phytoremediation works, what the real cost of the application will be, and how to build models to predict the interaction between plants and contaminants.

Some plants species have the capacity to withstand relatively high concentrations of several pollutants, such as heavy metals, without toxic effects. The tolerance to heavy metals in plants may be defined as the ability to survive in a soil/water that is toxic to other plants, and is manifested by an interaction between a genotype and its environment. Among the tolerant plants, the moss *Leptodictyum riparium* (Hedw.) (2, 4), and the floating aquatic angiosperm *Lemna minor* L. (1) have the ability to cope with the toxicity of heavy metals, and to uptake and accumulate these ions, raising the possibility of utilizing them for the removal of heavy metals from polluted waters.

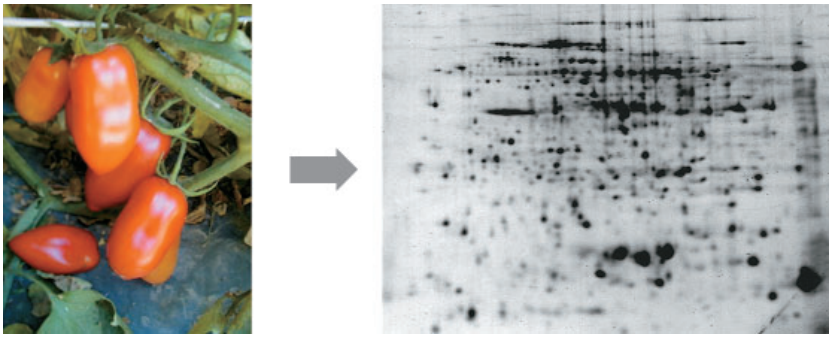
When plants are exposed to heavy metals, they respond to abiotic stress by accumulating an array of metabolites and by increasing the activities of enzymes involved in the detoxification of metals. Special focus has been given to the accumulation of phenols, to the HSP production and to phenylalanine ammonia-lyase (PAL) activity (1, 2, and work in progress) in the above mentioned species and in *Azolla filiculoides* Lam. exposed to different concentrations of heavy metals. Proteomic has been also applied to determine changes in protein synthesis due to the heavy metals toxicity in moss (4) and macrophytes (work in progress). *Azolla*, *Lemna* and *Pistia* capability to lower antimicrobial drug concentration, such as sulphonamide (Sulfadimethoxine) and quinolone (Flumequine), has been tested in laboratory models (3). The results obtained confirm the important role of these macrophytes in phytoremediation.

Part of the research has been undertaken in collaboration with the University of Naples "Federico II", Dipartimento delle Scienze Biologiche, Sezione di Biologia vegetale.

GROUP LEADER Mauro Marra ■ **STAFF SCIENTISTS** Lorenzo Camoni • Sabina Visconti ■ **PHD STUDENT** Chao Wang

Proteomic analysis of fruit ripening and quality

Fruit ripening is a key process in the production of the phytonutrients that are essential for a balanced diet and for disease prevention. The pathways involved in these processes are unique to plants and vary between species. Among fleshy fruits, tomato and apple are two of the most consumed worldwide. Molecular and genetic analysis of tomato ripening resulted in a significant gain of knowledge but a detailed biochemical profiling of the process is still largely unaccomplished. A deeper understanding of tomato ripening is highly desiderable also in view of possible manipulations for improving organoleptic and nutritional features. The tomato industry in the South of Italy has been largely based on S. Marzano ecotype which has become synonymous with excellent taste characteristics. Despite these highly desirable traits, S. Marzano cultivation recently had to confront the introduction of commercial elite varieties, which exhibited better field performances. Hence, understanding the underlying proteomics of fruit maturation, in addition to clarify ing the molecular mechanisms involved, will contribute to defining specific molecular markers for the selection of which breed varieties maintain the original desirable taste characteristics, and which are best suited to intensive cultivation. We have carried out a comparative proteomic investigation of tomato fruits from regional and commercial elite ecotypes during maturation. A number of proteins have been identified as differentially expressed during maturation. These proteins are associated to important physiological processes such as redox status control, stress, carbon metabolism, energy production and cellular signaling. Different apple cultivars are commonly available for consumers, although over the years only a limited number of elite varieties adapted to modern intensive cultivation, relegating many other cultivars to marginal production. The 'Annurca' apple is an IGP regional variety cultivated in Campania which produces fruits with peculiar flavour and aromas. Apple is a major source of dietary polyphenols and it has been reported that the content and composition of antioxidants varies greatly among cultivars. It has been demonstrated that flesh of Annurca fruits have a very high content of polyphenols. In a recent characterization of different accessions of Annurca cultivar, in relation to apple elite varieties, the genetic diversity of its germplasm clearly emerged. Integration of genetic data with the actual protein complement is highly desirable and informative for crop breeding and amelioration. This study concerned the first systematic proteomic analysis of the pseudocarp tissues of *Malus* x *domestica* Borkh. cv. Annurca. Mature fruits from three different accessions have been selected among the ones previously characterized at the gene level and compared for their protein repertoire. About fifty proteins related to important physiological processes such as energy production, ripening and stress response have been identified. The occurrence of allergens causing widespread food allergy syndromes was also detected.



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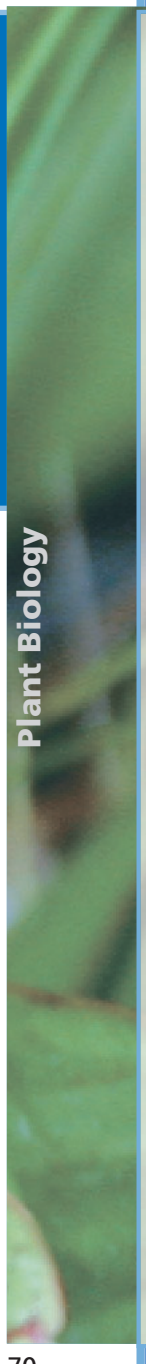
GROUP LEADER Alessandro Travaglini ■ **TECHNICAL ASSISTANT** Donatella Leonardi ■ **SCHOLARSHIP HOLDERS** Silvia Silvestri • Emanuele Sanapo

Aerobiological monitoring



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Aerobiology is a relatively young science that studies the particles, living and not (bacteria, algae, fungi, pollen, viruses, spores of ferns and mosses, insects and other microfauna, particles and gases generated by human activities and natural) present into the atmosphere, production sources, transport arrangements in the air and the effects on the environment (indoor and outdoor) in the first place in humans, but also on animals and plants.

The increased attention to environmental problems in recent decades, has highlighted to the study of particles of biological origin and artificial present in the atmosphere, often responsible for diseases borne by the human population, but also damage to property and artistic monumental and crops.

Aerobiological monitoring of airborne pollen allergy is particularly useful in the field of pollinosis. From a biological point of view, those that assume greater importance are the granules in particular pollen, fungal spores, actinomycetes, protozoa, products deriving from arthropods, viruses, bacteria, and algae.

These materials are the so-called organic aerosols, which can cause eziologic of disease. For this reason, aerobiology has been used for some time in allergology as a useful assessment tool for respiratory allergies.

The applications of aerobiological sampling (based on the count of grains of pollen and fungal spores) are different and have an important role in the diagnosis, prevention, control and clinical treatment of allergic patients.

Aerobiological monitoring allows to observe the concentration of pollen and spores in the city. The pollen crop is mainly produced from anemophilous plants and often is pollen allergen.

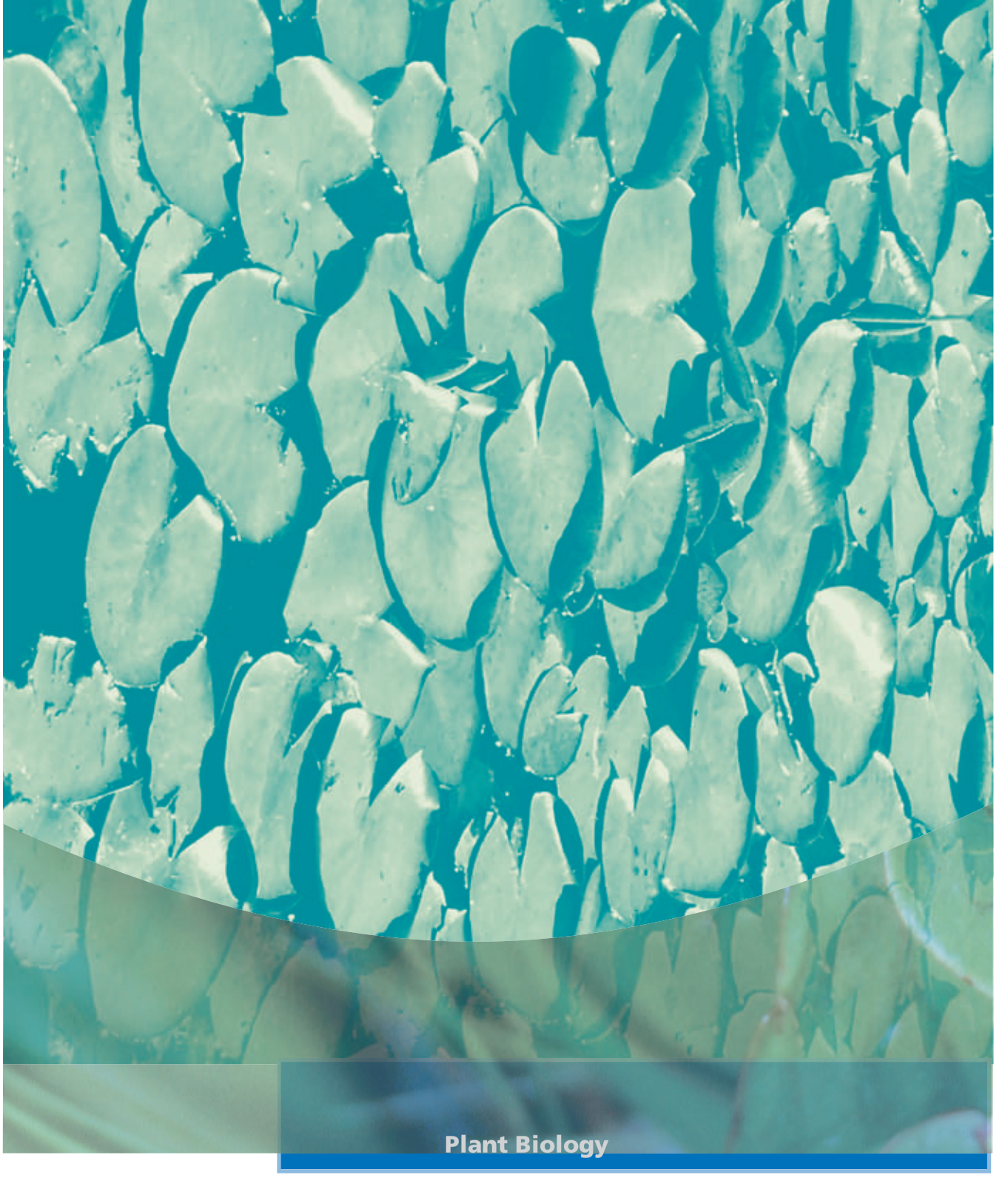
The aerobiological monitoring centre of the University of Rome Tor Vergata has been active since 1996 and coordinates the activities of other monitoring stations in the city.

The activity monitoring is continuous throughout the year and makes it possible to publish an on-line weekly newsletter featuring concentrations of pollen allergen interest www.uniroma2.it/biologia/polline.

Observations prolonged over time can follow the changes in early blooming, the peak value and total quantity of pollen issued. The series of historical data aerobiological and those weather constitute a useful tool in the study of climate change.

The observation was supported by observations on flora vegetation in the territory, especially in school gardens and sports facilities in order to reduce the presence of allergenic pollen in the air and improve the quality of life of allergic people, and set new guidelines in the design of these environments.

The palinological analysis also made it possible to carry out some forensic field-experiment in collaboration with the Biological laboratory of the Anti-Crime Dept. of the Italian State Police.



Plant Biology

Chapter six

Ecology

Nonnis Marzano C., Baldacconi R., Fianchini A., Gravina F., Corriero G. 2007. Settlement seasonality and temporal changes in hard substrate macrozoobenthic communities of Lesina Lagoon (Abulia, Southern Adriatic Sea). Chemistry and Ecology 23, 479-491.

GROUP LEADERS Eugenio Fresi • Stefano Cataudella ■ **STAFF SCIENTIST** Maria Flavia Gravina ■ **TECHNICAL ASSISTANT** Alessandra Fianchini

Characterisation and dynamics of brackish and marine coastal ecosystems

Several biological methods have been assessed in order to estimate the environment quality and evaluate the impact of the main human activities on aquatic ecosystems.
Most of biological criteria are based on the concept of "biological indicator", which includes organisms, or groups of organisms, which show biological reactions considered particularly suitable for estimating environmental conditions. The Agenda 21 (United Nations Conference on Environment and Development – Rio de Janeiro, 1992) proposes the identification of indicators useful to measure the effects of human activities on natural resources.
Benthic communities are useful biological indicators in complex environmental conditions, which are mostly influenced by a lot of causes, measurable with difficulty by other methods.
Several human interests (naturalistic, productive, recreative, tourist, business) come together in brackish environments. Such environments are highly productive and have been exploited for human activities from time immemorial. Besides, they usually have a short geological life and their management allowed their conservation. The use of biological indicators in brackish systems has been recently focused and such indicators have proved a useful means for evaluating the deviations in structure and function of ecological characteristics, with respect to reference conditions, and thus for monitoring the environments and for giving information on management of such ecosystems.
In this research macroorganisms living on soft and hard substrates in the lagoons of South Adriatic Sea (Lesina, Acquatina) and of Albany (Karavasta, Butrinti, Kune) have been studied, in collaboration with the Universities of Bari and Lecce, where some results of previous studies on such environments are already available.
In marine ecosystems the benthic communities have been studied in order to preserve biodiversity in the Marine Protected Area "Tor Paterno" Tyrrhenian Sea (Lazio). The marine protected areas are established to protect a certain species, to benefit fisheries management or to protect full ecosystems, rare habitats, or nursery grounds for fish. The benthic communities have been also analysed in the Biological Protection Zone (Zone di Tutela Biologica) which have been designated in order to support the reproduction and growth of fish species of ecological and economic importance.

GROUP LEADER Michele Scardi

Artificial neural networks applications in Ecology and Oceanography

Neural networks (or, according to a more correct definition, artificial neural networks) are very powerful and flexible computational tools, that can be used in a wide variety of applications, like, for instance, classification, pattern recognition, generalized regression and empirical modelling.
Although these tools have been recently introduced in ecological and oceanographical research, the number of their applications is rapidly growing and they very often outperform other methods. Some of the applications that have been developed or that are under development in our Group are the following: phytoplankton primary production assessment (both at global and at regional scale), calibration of oceanographical probes, prediction of the concentration of pollutants in marine sediments, prediction of community structure, analysis and classification of faunistic and floristic lists, etc.
Even though the main research activity is focused on neural networks, other Artificial Intelligence and Machine Learning tools are also routinely applied in order to design new ecological applications that allow significant advances relative to conventional approaches.
Prof. Scardi is a founding member of the International Society for Ecological Informatics and a member of the Editorial Board of the Ecological Informatics journal (Elsevier).
Additional information on this research topic is available at the following URL: http://www.mare-net.com/mscardi/work/nn/nn.htm.

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GROUP LEADERS Michele Scardi • Eugenio Fresi

Statistical analysis of ecological data

The statistical analysis of ecological data has become a fundamental component of the ecological research during the last 20-30 years. Although people tend to consider ecology as a discipline that is based on a purely naturalistic approach, there are very few other disciplines in which mathematical and statistical tools play a more relevant role. This peculiarity inspired the development of original methods for data analysis that have been eventually applied in other fields.
The data sets that are gathered during research and monitoring activities both in marine and terrestrial ecosystems are usually multivariate and do not fulfill all the requirements that have to be met in order to apply parametric statistical methods. This is the reason why tools for statistical analysis that are particularly effective in summarizing the available information as well as tools for testing ecological hypotheses are so relevant in ecological research.
Researchers in our Group were among the first users and developers of these tools in Italy, more than 25 years ago. This activity has continued ever since and has been improved and enriched by new tools, taking profit from the development of informatics, making it possible to widen the range of the potential applications.
More information on this topic is available at the follwing URL:
http://www.mare-net.com/mscardi/work/numecol/numecol.htm.

GROUP LEADER Michele Scardi ■ **STAFF SCIENTIST** Lorenzo Tancioni

Evaluation of ecological status of streams and rivers

The present EU policy about the assessment of water quality (see Directive 60/2000/EC, aka Water Framework Directive) emphasizes the role of the study of aquatic communities. In particular, fish assemblages, as well as other groups of organisms, are among the biotic quality elements that have to be taken into account for the assessment of the ecological status of streams and rivers.
In the recent past many biotic indices have been developed in order to assess environmental quality in ecosystems that sustain particular environmental conditions and anthropic pressures. Even though this approach make it possible to easily evaluate the overall environmental quality, it has inherent limits, as it can be too simplistic and insufficiently revealing.
The main issue of this consideration is that the overall structure of aquatic communities rather than the biotic indices is to be regarded as a benchmark for evaluating the quality of the environment as a whole. In particular, the most frequently used components (and to which the above mentioned directive refers) are fish fauna, benthic macroinvertebrates and aquatic flora (benthic diatoms and macrophytes). Each component returns a different picture of the ecological properties of a given biotope and integrates that picture over a different spatial and temporal scale.
In this framework, the prediction of the community structure plays a major role, as no absolute ecological quality assessment can be obtained if an expected reference community structure (i.e. the one that is expected under unperturbed conditions) cannot be defined. Even in this case, scaling the quality assessment is still based on subjective assumptions.
Our work is aimed at defining methods for assessing the ecological status (*sensu* Water Framework Directive), especially using fish fauna as the main biotic quality element. An expert system (FIDESS – Fish-based Decision Support System) has been recently developed to tackle this problem, comparable with other European methods in the framework of the EU intercalibration activities, on behalf of the Italian Ministry of the Environment and Environmental Protection Agency (APAT). Software, papers and reports can be downloaded from:
http://www.michele.scardi.name/fidess.zip

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GROUP LEADER Stefano Cataudella ■ **STAFF SCIENTIST** Caterina Lorenzi ■ **PHD STUDENT** Riccardo D'Eramo

Environment education and didactics of ecology in primary school and in university courses for primary school teachers

Primary school teachers' low level of science knowledge and their lack of confidence in teaching science are documented at length in many western countries. Such deficiencies interest particularly the ecological fields. We propose advanced educational approaches for in training primary school teachers looking at the methodological guidelines of the national and international school curricula. Didactics of ecology and environmental education are proper fields to test new active/cooperative learning strategies. Moreover, environmental education offers frequent linkages to different disciplines as mathematics, geography and literature and can be used as a didactic framework for transdisciplinary studies.

GROUP LEADER Stefano Cataudella ■ **STAFF SCIENTISTS** Clara Boglione • Emilia Cataldi ■ **POST-DOC** Irene Ferrante ■ **PHD STUDENT** Ayad H. Dawood

Morphophysiological studies on euryhaline fish

This research contributes, at a basic level, to the understanding of the complex mechanisms involved in water and ions homeostasis in euryhaline fish.
At an applied level, it provides information on the optimal conditions, *i.e.* low stress situations, for the acclimation of species for fish farming or restoration/restocking, to environments characterised by variable salinity.
In this group, the following studies are included:

- Comparative morphophysiological studies on the osmoregulatory organs of mullets at different salinity. The aim is to clarify an aspect of Teleost osmoregulation: the mechanism limiting homeostatic adaptation to different salinity ranges. Mugilidae have been chosen because of the interspecific differences in euryhalinity.
- Studies on health/stress indicators, and on stress conditions for reared fish. Transport, handling, hypoxy, crowding, habitat and social interactions are undoubtedly a stress for reared fish, whose effects can be responsible of sub-lethal effects, damaging the quality of fish product. In fact, stress activates the hypothalamo-pituitary-interrenal axis, inducing abnormal release of corticosteroids and catecholamines and consequently, neuro-hormonal disorders. The latter can jeopardise many physiological functions, negatively affecting metabolism, and hence growth, reproduction, resistance to pathologies and, also, flesh quality and its deterioration. Therefore it is important, in the framework of a scientific approach to aquaculture, to consider indicators that can promptly detect stress factors, to measure responses and to evaluate recovery time. Stress in fishes can be routinely detected by measuring changes in some blood parameters, if the standard set of reference values is assessed for each species, and if standard sampling procedures can be set out without altering blood levels of these parameters.

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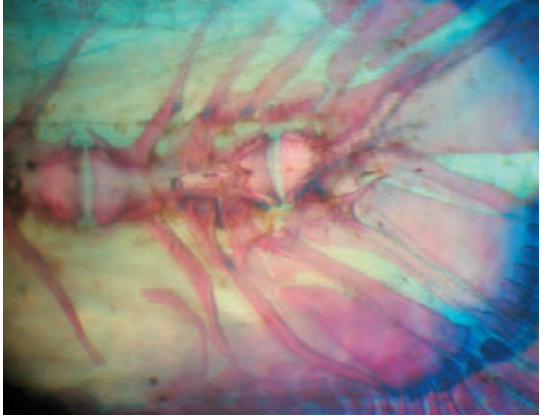

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GROUP LEADER Stefano Cataudella ■ **STAFF SCIENTIST** Clara Boglione

Studies of skeletal anomalies in fishes as markers of environmental quality

Typology and relative frequencies of anomalies are studied in Mugilidae, Clupeidae, Moronidae and Sparidae, in natural environments, thus contributing to identify cause-and-effect relationships between anomalies and environmental impacts in wild fish populations. The method relies on the assumption that environmental changes due to heavy metals, PCP etc. affect the correct skeletal development in fishes. Therefore, high frequencies of critical teratologies can be considered a marker of environmental damage that occur in nursery areas in the coastal zone.

GROUP LEADER Stefano Cataudella ■ **STAFF SCIENTIST** Emilia Cataldi ■ **POST-DOC** Irene Ferrante

Researches on the oxidative stress in the ecology and evolutionary biology marine and freshwater fish

This research line makes a contribution at both a basic and at an applied level. At the former level, studies on the mechanisms involved in controlling oxidative status and antioxidant compounds are carried out, as well as studies targeted at the identification of oxidative stress markers, comparing ecologically or phylogenetically different species, in order to evaluate specific responses. The latter aspects concern the identification of antioxidant compounds, whose variations in fish tissues can represent an indicator of oxidative stress, as related to vulnerability to diseases, aging or exposure to certain environmental factors such as pollutants. Main applications apply to sea food quality and fish health assessment.

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Ecological studies of Teleost fishes

This research topic includes the study of many aspects of the ecology of Teleost fishes, used for resource management and conservation. These studies, still in progress, include investigation into both fish trophic ecology and population dynamics of riverine fishes, and can be utilised to assess the ecological status of riverine environments. Another line of research concerns the ecology of lotic fish assemblages in regulated streams and rivers, with particular regard to the selection of methodologies for minimum flow assessment in rivers of Central-Italy. Attention is primarily focused on reophylus Ciprinids (barbel and chub), in the low reaches of the River Tiber. In this river, a permanent "observatory" for fisheries and aquatic ecosystem are the goals of a project financed by the Province of Rome.

GROUP LEADER Stefano Cataudella ■ **STAFF SCIENTISTS** Lorenzo Tancioni • Eleonora Ciccotti

Applied research for aquatic resource management

Research in this field deals with the optimisation of aquaculture models integrated in the agricultural context, such as phytodepuration systems of intensive breedings' waste waters and rearing techniques of freshwater species. The establishment of low-impact aquatic production systems is consistent with both principles of ecocompatibility, biodiversity conservation and models of sustainable development. This last framework includes other research aimed at setting up models of responsible use and management of aquatic living resources. For many years the research group has conducted a monitoring project at national level on eels, *Anguilla anguilla*, a commercial species that requires a specific management strategy. In fact, this species is migratory marine with significant stocks in inland waters of many countries, and must therefore be considered a shared resource needing a supranational setting.

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GROUP LEADER Stefano Cataudella ■ **STAFF SCIENTIST** Clara Boglione ■ **POST-DOCS** Tommaso Russo • Corrado Costa

Studies on growth patterns and morphological variability in larvae and juveniles of wild and reared fishes through image analysis and geometric morphometric tools

Rapid data acquisition and the way of collecting data with remote systems both make acquisition procedures and image analysis powerful tools in the study of growth patterns and in the determination of morphological variability of wild and reared fish populations. This research topic using dual camera systems and image analysis softwares allows, through the remote monitoring, the three-dimensional reconstruction of the outline of form. The study of fish shape, as a higher level of phenotypic integration, through geometric morphometrics and outline fitting methods can support quality assessment techniques of larvae and juveniles from natural and artificial systems, offering quick responses and high resolution.

GROUP LEADER Stefano Cataudella ■ **STAFF SCIENTISTS** Clara Boglione • Emilia Cataldi ■ **POST-DOCS** Corrado Costa • Irene Ferrante • Maurizio Giganti • Tommaso Russo ■ **PHD STUDENT** Riccardo Caprioli

Studies on the reproduction of "new candidates" for fish culture

New species (*Epinephelus marginatus, Seriola dumerilii, Pagellus erythrinus, Diplodus puntazzo)* for fish culture are considered not only with regard to the definition and refining of induced spawning techniques, but also in studies concerning the embryonic and larval development, with special emphasis on the ontogenesis of skeletal, sensorial and digestive apparatus. The anatomical status of the juveniles is then compared with wild specimens in order to evaluate its quality on the basis of the morpho-anatomical resemblance with the wild reference. This topic is related to studies on the effects of manipulation on the development of skeletal structures; it is also as a support to the optimisation of the reproduction techniques. Furthermore, the study of development of skeletal, digestive and sensorial apparatus can provide information on larval trophic behaviour in the wild. Different ontogenetic sequences of sense organs development reflect different trophic and ecological strategies, these organs being involved in food detection, selection and ingestion.
Also bluefin tuna (*Thunnus thynnus*) is considered in the activity of this research group. In fact, the expansion of the fattening industry makes bluefin tuna overfished and wild stocks threatened. In this situation, a great interest grew in the last years in studying the feasibility of developing aquaculture technology for tuna reproduction and domestication. In particular, the research group carried out studies on morphology of digestive tracts in wild tunas, on reproductive status in wild and captive tunas, on the stress condition of tuna in cages, and on the possibility of developing a stereo video system, in association with an effective ANN algorithm, to provide tuna images inside the fattening cages. These studies were aimed to:

- improve our knowledge on the reproductive biology of the species
- assess the capability of BFT broodstock to mature and spawn in captivity
- assess the effects of long and short captivity on reproductive maturation
- estimate the number, size and biomass of BFT, thus validating the potential advantages of the use of underwater video monitoring noted by ICCAT (2004).

GROUP LEADER Stefano Cataudella ■ **STAFF SCIENTIST** Clara Boglione
■ **POST-DOC** Maurizio Giganti ■ **PHD STUDENTS** Chiara Rocchi • Domitilla Pulcini

Larval and juveniles quality assessment in fish species from controlled reproduction

Rare and frequent anomalies occurring in artificial environments in sea bass (*Dicentrarchus labrax*), sea bream (*Sparus auratus*), amberjack (*Seriola dumerilii*), pandora (*Pagellus erythrynus*), sharpsnout seabream (*Diplodus puntazzo*), common seabream (*Pagrus pagrus*), common dentex (*Dentex dentex*), thick lipped mullet (*Chelon labrosus*), grey mullet (*Mugil cephalus*), perch (*Perca fluviatilis*), barbel (*Barbus barbus plebejus*), trouts (*Salmo trutta macrostigma*, *Oncorhynchus mykiss*) are studied by relating physical descriptors of environmental conditions with the onset of anomalies. This research topic contributes both to the study of embryology and larval ontogenesis of Teleost fishes (with particular emphasis to the skeletal development) and to the optimisation of productive processes in aquaculture. Its contribution at a basic level concerns the knowledge of the embryology and skeletal development of Teleost fishes, and at an applied level it can contribute to the optimisation of productive processes in aquaculture. Variations in meristic counts, as well as in the morphology of individual bony components, can be used as a "markers" of the larval development conditions, strictly connected with variations of development homeostasis. The greater the degree of morphological variation from the standard reference, the higher is the level of genetic and/or epigenetic disturbance during larval development. Practical applications of this approach are related to the definition of product quality within the framework of a Responsible Aquaculture (as indicated by the FAO Code of Conduct for Responsible Fisheries), and for the establishment of a certification protocol for Organic Fish. Furthermore, this approach can be used for the evaluation of new diets or new rearing technologies, and to discriminate reared and wild fishes in the course of restocking in lagoon environments, to assess the restocking performances.

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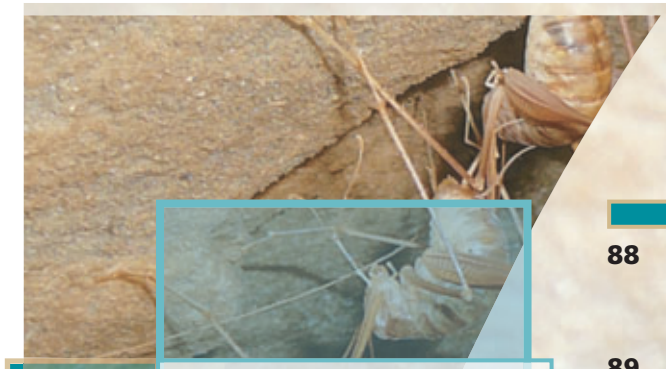
GROUP LEADER Stefano Cataudella ■ **STAFF SCIENTISTS** Clara Boglione • Lorenzo Tancioni • Eleonora Ciccotti • Emilia Cataldi

Establishment of a Laboratory of Communication and Evironmental Education

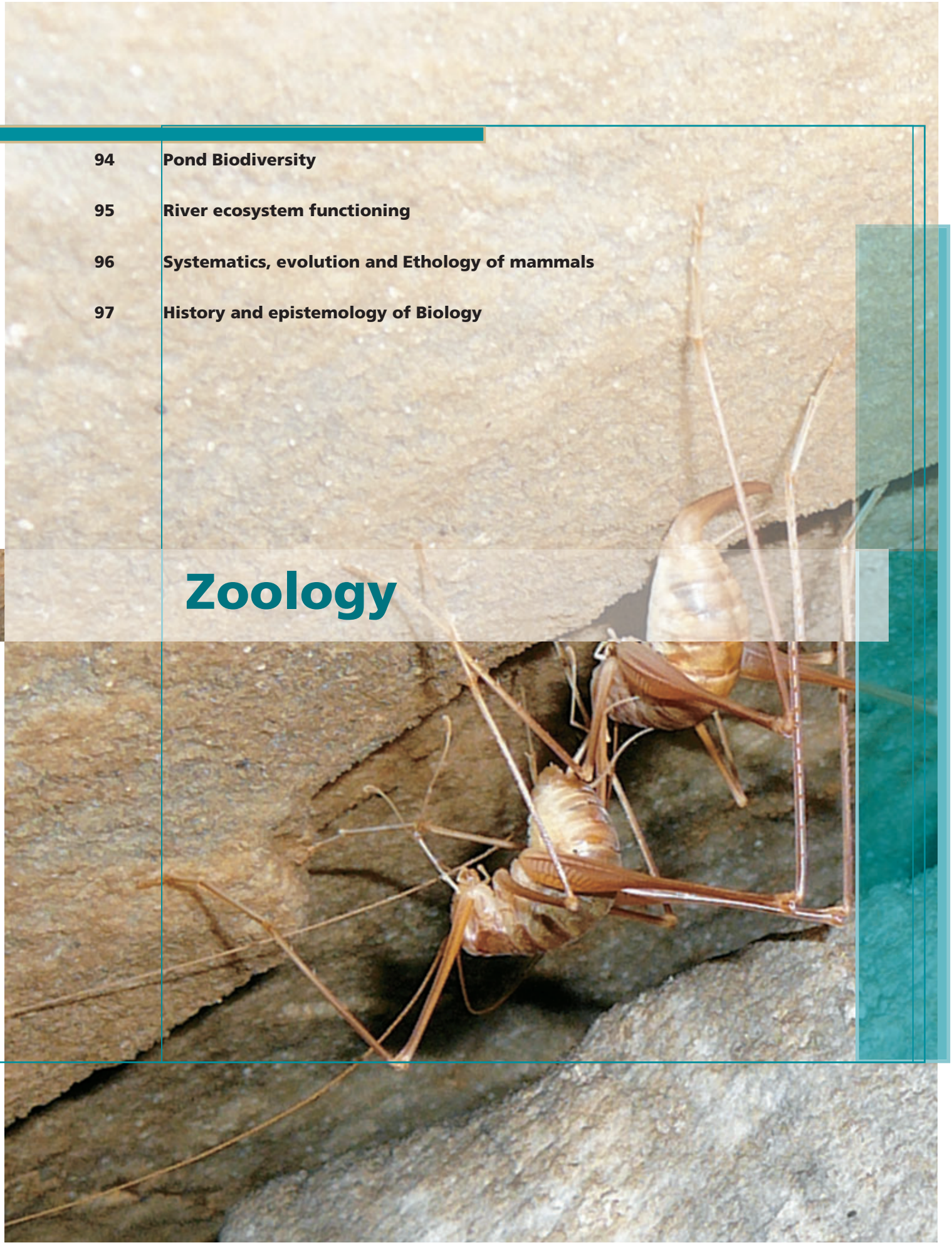
All research themes fit into a global framework, answering to the need for new patterns for living aquatic resources exploitation, are based on sustainability criteria and on a responsible resources use. Environmental Education is an important part of this framework; for this reason for many years it has been one of the activities of the Experimental Ecology and Aquaculture Lab. This discipline is carried out in the form of environmental education paths focused on aquatic systems ecology and on the responsible use of aquatic living resources, intended for schools in collaboration with the Comune di Roma within the Programme "Città come Scuola". Up to now, over 10.000 students from 300 schools in Rome have visited the Experimental Ecology and Aquaculture Centre. Furthermore, recently a Laboratory of Communication and Environmental Education has been established, with the task of fostering responsible conduct in the use of aquatic living resources, together with Fishery Associations and Consortia of the fishery sector.

Ecology



Chapter seven

Zoology



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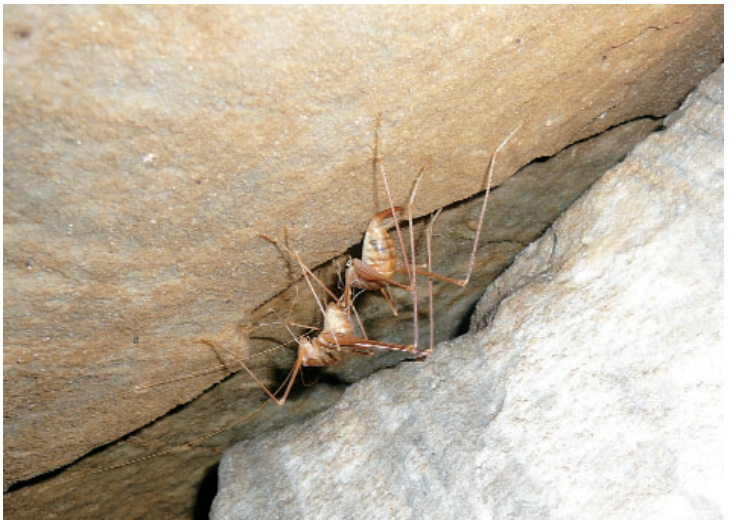
GROUP LEADER Valerio Sbordoni ■ **STAFF SCIENTISTS** Giuliana Allegrucci • Fabiola Baldari • Donatella Cesaroni • Gabriele Gentile • Marco Lucarelli

Natural history and evolutionary studies of cave organisms

Organisms adapted to cave life are of great interest for the study of evolutionary processes. Actually, specific adaptation processes expressed at morphological and physiological levels are replicated with similar modalities in different organisms and in different areas. For this reason, caves are considered as a natural laboratory where spatial isolation, habitat peculiarity, relatively simple ecosystem features, and the restricted population size make experimental research and modelling of microevolutionary processes feasible.
Our group investigates the structure of cave populations with a specific focus on the genetic consequences of habitat's and isolation's fragmentation processes. This research is carried out by estimating evolutionary parameters such as the amount of genetic variation in populations, the degree of gene exchange among populations (genes flow), the strength and efficacy of selection and the evaluation of evolutionary divergence ratio between two organisms with a common ancestor. Cave populations are an appropriate experimental support for analysing and validating these parameters.
Genetic structure is investigated by using multiple molecular markers. Data are analyzed by means of different multivariate statistical techniques which allow multidimensional classification and ordination analysis, by means of geostatistic techniques of geographic representation as well as by tools specific for population genetic and phylogenetic inferences.
Dolichopoda cave crickets are the animal model best studied: cladogenetic events, reproductive isolation factors among different species (in cave laboratory experimental breeding) are investigated by using molecular phylogeny and phylogeography, while natural and experimental colonization events, population's size assessment and genetic variability analysis are investigated by means of nuclear microsatellites selected for the purpose.



GROUP LEADER Valerio Sbordoni ■ **STAFF SCIENTISTS** Donatella Cesaroni • Marco Lucarelli • Saverio Forestiero ■ **PHD STUDENTS** Tania Deodati • Paolo Gratton • Manuela Pinzari • Valentina Todisco

Systematics, zoogeography, molecular phylogeny and conservation of Butterflies

Our laboratory is currently involved in wide-ranging studies on the population genetic structure, phylogeography and phylogeny of several butterfly species of conservation concern.
A first project focuses on patterns of genetic variation in populations of the montane butterflies *Parnassius mnemosyne* and *P.apollo*, displaying similar Centroasian-European distributions, but different ecological requirements. Accurate reconstruction of their phylogeography offers a unique opportunity for comparative analyses investigating the influence of past climate changes in assembling the diversity of European biotas. Phylogeographic analysis of mitochondrial DNA sequences (COI) showed that *P.mnemosyne* populations bear genetic traces of a geographic history about one million years long.
Highly divergent mitochondrial lineages mark at least two Evolutionarily Significant Units in Europe. Bayesian coalescent approaches were applied to provide a detailed depiction of the history of European populations through the Pleistocene. Phylogeographic patterns and paleoecological data have been combined to calibrate a new intraspecific substitution rate. The latter result may represent a highly relevant by-product of this research and find application in other studies on Lepidoptera. The distribution of COI sequence diversity in *P.apollo* reveals that in Europe this species experienced different waves of range expansion and fragmentation in the recent past, and the low levels of genetic variation suggest that it may represent a relatively new invader in Europe. A comparative analysis of *P.apollo* and *P.mnemosyne* Italian populations showed that the two species followed similar patterns of colonization in different epochs: while *P.mnemosyne* left its glacial refugia after forest advance in the Holocene, *P.apollo* was able to expand its range through the most extreme glacial stages by taking advantage of extensive steppe-like habitats.
Another research project is aimed at investigating molecular systematics and evolution of butterflies with Sino-Himalayan distribution. The Sino-himalayan mountain ecosystems are of unique global significance as biodiversity "hot spots" and represent a transition zone of special interest because here Palaearctic and Oriental biotas overlap and several taxa are exclusive. Research on taxonomy, molecular phylogeny, zoogeography and mtDNA COI sequences for "DNA Barcode of Life project" are currently in progress for several species belonging to different genera and distributed from the tropical zones in Nepal and Yunnan up to over 5000 m in Tibet, showing a high degree of evolutionary novelty. Results of the investigations on the "Callerebias" group of butterflies strongly suggest their Palaearctic rather than Oriental origin, as had long been supposed.

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GROUP LEADER Valerio Sbordoni ■ **STAFF SCIENTISTS** Donatella Cesaroni • Gabriele Gentile • Giuliana Allegrucci • Marco Lucarelli • Marco Mattoccia • Fabiola Baldari • Anna Fabiani • Stefano De Felici • Massimo Di Rao ■ **PHD STUDENTS** Paolo Gratton • Antonio Romano • Emiliano Trucchi

Conservation Biology and Biodiversity Management

The Department of Biology is involved in a number of projects as the primary set up and/or in collaboration with other Institutes and Universities. For example, we lead a project of conservation genetics of the land iguanas from the Galápagos. As a result of direct human activity and introduction of exotic forms many land iguana populations became extinct in several areas of the archipelago. Thirty years ago, in order to save the Galápagos land iguanas, the Galápagos National Park Service (GNPS) started a program in collaboration with the C. Darwin Research Station (CDRS) aimed at (1) eradicating exotic species, (2) restoring threatened land iguana populations, and (3) reintroducing land iguanas into areas where they had become extinct. Through the molecular genetic characterization of all the surviving populations of land iguanas, our project is aimed at providing the necessary data for an efficient program of restoration and reintroduction of endemic land iguanas in the Galápagos Islands. Genetic data are integrated with information from veterinarian, parasitological, biochemical, hormonal, and microbiological analyses to assess the welfare status of land iguanas populations. We also collaborate with the University of Ferrara in a project aimed at claryifing the phylogeography of spur tortoises belonging to the genus *Testudo*. The project aims at the identification of origin and the degree of admixture of natural populations.
We coordinate the "Osservatorio Regionale per la Biodiversità", a structure for the analysis of the biological diversity of Lazio, in collaboration with the other Universities of the region. The Observatory consists of a geo-database dedicated to recording, sharing and linking biodiversity data, and to allowing on-line analysis tools. It is associated to the Regional Agency for Protected areas (ARP) and connected with the Regional Information System for the Environment (SIRA).
The Observatory is also involved in the identification and estimation of the different values of biodiversity of Latium with special regard to their ecological, historical and biogeographical context; the monitoring of biodiversity at different levels (genes, species, habitats) in the "Natura 2000" network, and in the assessment of guidelines for the monitoring of biodiversity. In recent years the Observatory team has participated actively in the the management planning of the largest Latium areas of the European Natura 2000 network: SPZ Tevere-Farfa, SPZ Monti Ernici e Simbruini and included SCI, SPZ Monti Aurunci and included SCI, SPZ Monti Lucretili and included SCI, SCI Grotta di Bellegra.

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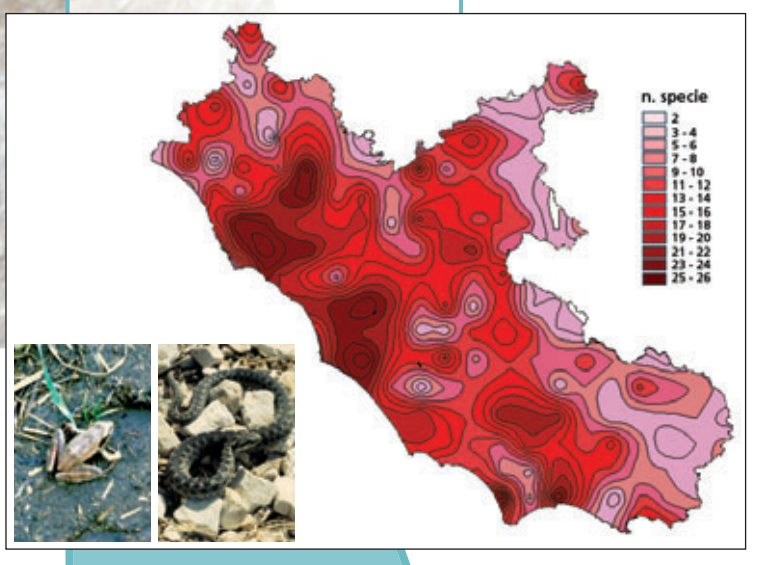

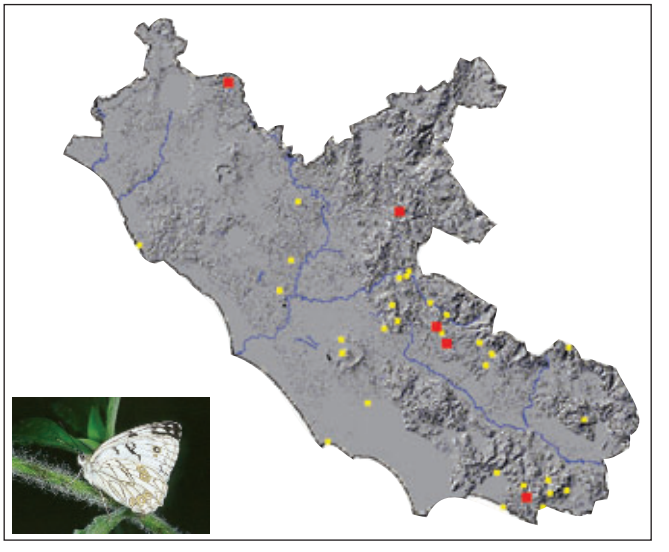

GROUP LEADER Valerio Sbordoni ■ **STAFF SCIENTIST** Marco Mattoccia
■ **PHD STUDENTS** Antonio Romano • Silvio Marta

Biology, Ecology, and Genetic Structure of Amphibians

Major concern is caused by the observed decrease in the number of amphibians. Species which show limited distribution and narrow habitat constraints are particularly affected by reduced gene flow between more and more isolated populations and this ultimately leads to a high risk of extinction. We started research aimed at addressing the conservation of *Bombina pachypus* and *Salamandrina terdigitata*, particularly in some areas of Latium, by both performing a faunistic investigation and combining data from ecology and population genetics. These two species are both endemic to Italy. In particolar, for *B. pachypus*, a long-term study is being carried out to monitor reproduction in natural populations from the Lepini Mountains. Secondly, our study on *Salamandrina*, by using sequence data of three mtDNA genes, revealed the extistence of two separate evolutionary lineages that deserve their own taxonomic status.

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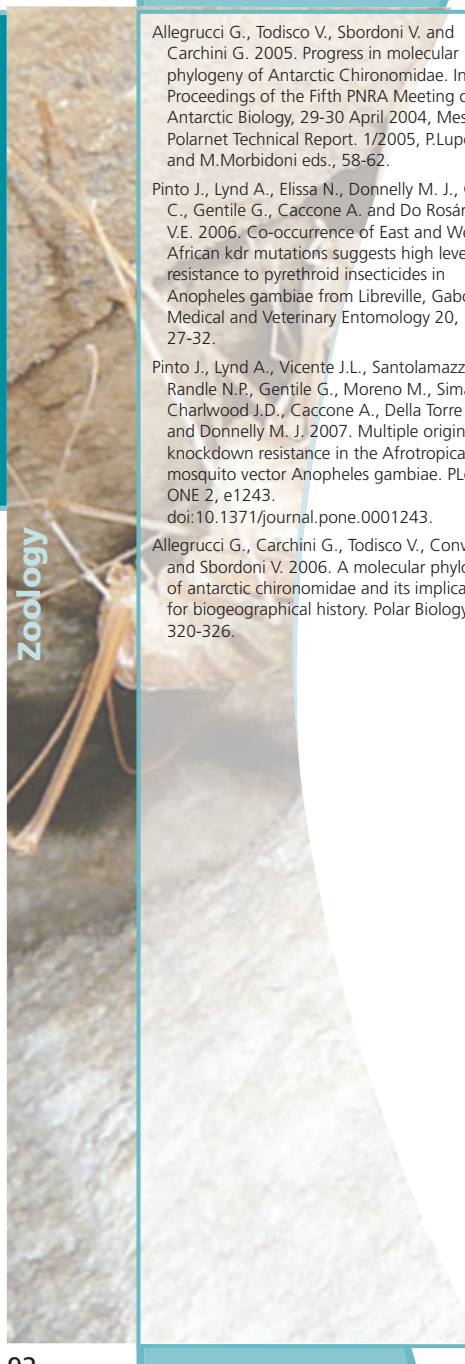

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GROUP LEADER Valerio Sbordoni ■ **STAFF SCIENTISTS** Giuliana Allegrucci • Gianmaria Carchini • Gabriele Gentile ■ **PHD STUDENT** Valentina Todisco

Molecular phylogeny and speciation in Insects

In collaboration with the Yale University and the Dept. of Science of Public Health, Section of Parasitology, University La Sapienza, speciation processes have been studied in *A.gambiae* s.s., one of the most important vectors of malaria.
This project aims at the study of chromosomal/molecular forms of *A. gambiae,* the goal being to clarify their geographic distribution, genetic isolation and taxonomic status. Another project, in collaboration with the Dept. of Science of Public Health, Section of Parassitology, University La Sapienza, aims to study introgression of the resistance to pyrethroids in sub-Saharan populations of *A. gambiae* and *A. arabiensis*.
Chironomid midges *Belgica antarctica*, *Eretmoptera murphyi* (subfamily Orthocladiinae) and *Parochlus steinenii* (subfamily Podonominae), are the only Diptera species currently found in Antarctica. The relationships between these species and a range of further taxa of Chironomidae were examined by sequencing domains 1 and 3–5 of 28S ribosomal RNA. The divergence dates obtained, using the molecular substitution rate available for Diptera, were 49 million years (Myr), between *B. antarctica* and *E. murphyi*, and 68.5 Myr between these species and the closest Orthocladiinae taxon tested from Patagonia, suggesting that *B. antarctica* and *E. murphyi* were representatives of an ancient lineage. As both are endemic to their respective tectonic microplates, their contemporary distribution is, therefore, likely to have been shaped by vicariance rather than dispersal.

GROUP LEADER Gianmaria Carchini ■ **STAFF SCIENTISTS** Antonio Ruggiero • Lorenzo Proia ■ **PHD STUDENTS** Marco De Cicco • F. Lacasella

Studies on Taxonomy, Ethology and Ecology of Odonata

The study of the taxonomy of larval stages of African Odonate has been continued. Studies on relationships between the reproductive success of males, assessed by Lifetime Mating Success, and individual characteristics such as fluctuating asymmetry and size, have been continued too.
The relationships between the presence of odonate species and environmental variables were examined in groups of ponds in nature reserves both in lowland and in montane areas. These studies demonstrated that the species richness is negatively related with the eutrophication, and positively with the abundance of aquatic vegetation.

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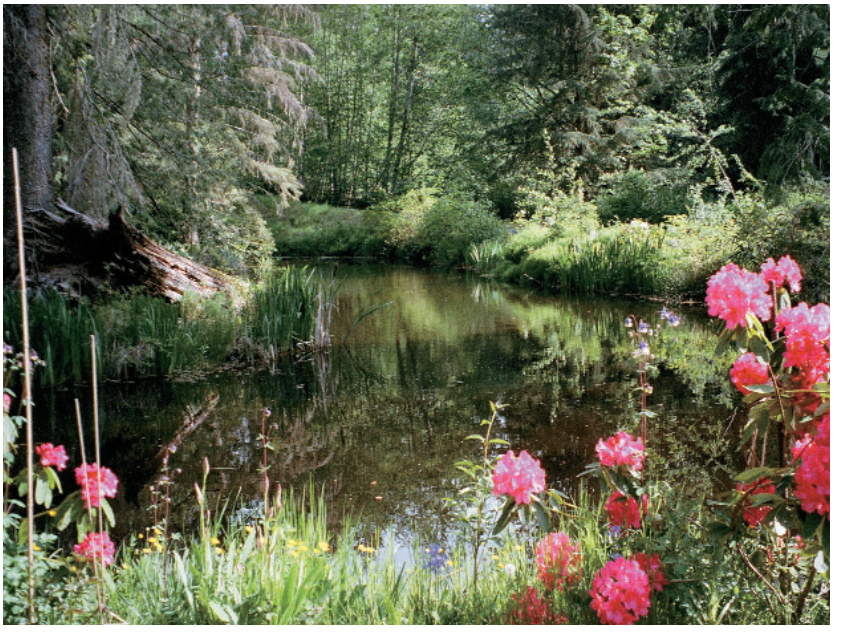
GROUP LEADER Gianmaria Carchini ■ **STAFF SCIENTISTS** Antonio Ruggiero • Lorenzo Proia ■ **PHD STUDENTS** Marco De Cicco • F. Lacasella

Pond Biodiversity

Still waters of small size were investigated. Studies on relationships between macrobenthonic community and environmental conditions in that habitat were made in order to elucidate the role of ponds in maintaining the invertebrate biodiversity. From original data collected in previous studies, a model linking the alternative stable concept and pond management was defined.



GROUP LEADER Gianmaria Carchini ■ **STAFF SCIENTISTS** Antonio Ruggiero • Lorenzo Proia ■ **PHD STUDENTS** Marco De Cicco • F. Lacasella

River ecosystem functioning

For running water, especially streams of lower order, experimental studies were carried out on ecosystem functioning, with special reference on nutrient retention, in streams under different pollution conditions. Besides this, the effects of small dams on both physico-chemical conditions and biotic communities of small rivers were studied.

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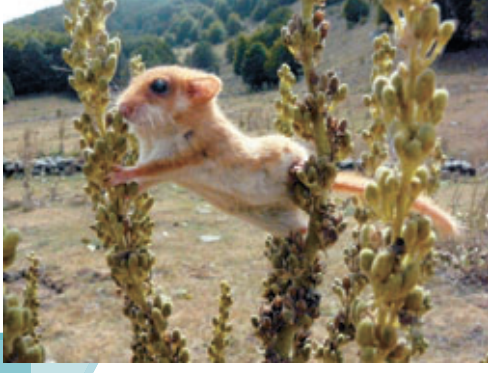

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GROUP LEADER Maria Grazia Filippucci ■ **STAFF SCIENTIST** Monica Carosi

Systematics, evolution and Ethology of mammals

Insectivora, Rodents and non-human Primates are the subjects of investigation in this area of research.
In our Department, a long lasting project has been running, focussed on Insectivora and Rodents, which display different evolutionary strategies of speciation and ecology. A study of their morphological and genetic variation in the different districts of the area has been carried out by morphometric, cytogenetic and electrophoretic analyses. A multidisciplinary approach was needed to detect the sibling species which are so frequent among small mammals and so difficult to recognize by morphological characters. These studies made it possible to understand the original and the present structure of European mammal fauna as well as that of the occidental Palaearctic area. The results have been used to study microevolutionary processes involved in speciation. The main aims of the ongoing research can be grouped as follows: a) to define the taxonomic position of many species of Rodents and Insectivora of the Mediterranean area; b) to study genetic variation and speciation in fossorial mammals; c) to compare genetic variation in small mammals.
More recently, a new line of research started, which focuses on the multimodal communication by female and male primates in the reproductive context: the adaptive significance of specific sexual signaling. In the study of primate communication is crucial to consider behavioral expression as the outcome of an integrated exchange of multiple sensory signals. Visual, chemical (olfactory/gustatory), and auditory types of communication likely occur simultaneously on many occasions, requiring the body to coordinate efforts in both generating and receiving various signals. In Neotropical arboreal primate species chemical and auditory signals are faithful companions of behavioral interactions and behavior itself may turn into the most conspicuous signal for females to advertise her fertile phase of the cycle while monopolizing the male attention (e.g., *Cebus* species). In Old World semi-terrestrial primate species, females of a few species advertise the fertile phase by a reddening and a conspicuous swelling of the anogenital area. However, this extraordinary visual signal (in some species up to 25% of the whole body weight) is apparent over an extended period of time that lasts way beyond the day in which ovulation occurs. In *Macaca tonkeana*, an endemic primate species of Sulawesi Island (Indonesian archipelago) sexual swelling may last up to 20 days in a 35-day ovulatory cycle. The adaptive significance of this exaggerated visual signal in terms of a) its information content (reproductive status, stress/parasite health condition), and b) effects on the receiver (mate choice, sperm competition, sexual motivation) is currently under investigation, in collaboration with ETHOIKOS and Associazione Giardino Faunistico di Piano dell'Abatino (GFPA). A multidisciplinary approach is used which includes behavioral data, non-invasive analysis of steroid hormones (from fecal samples), quantitative morphology, the study of genetic variability at the MHC loci (non-invasively sampled by using hairs and/or feces), fecal parasitological count. Results are interpreted in a broad comparative perspective by integrating species phylogenetic relations and diversified socio-ecological conditions which might have shaped species signaling differences.

GROUP LEADER Saverio Forestiero

History and epistemology of Biology

A historical and critical investigation of evolutionary biology's and ecology's key-ideas, such as Adaptation and Environment, is in progress as well as the study of the biological complexity's specific characters.

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Chapter eight

Immunology and Virology

GROUP LEADER Luciana Migliore ■ **STAFF SCIENTISTS** Maria Cristina Thaller • Cinzia Forni ■ **POST-DOCS** Eva Alessi • Daniela Mattei ■ **PHD STUDENTS** Maurizio Fiori • Alice Rotini

Ecotoxicology: tools for environmental monitoring and effects of contaminants (i.e., antimicrobials)

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Antimicrobial drugs utilized in intensive farming can impact on environmental compartments such as water and/or soil. Previous studies demonstrated their persistence in environmental compartments, where they can produce biological effects ranging from direct toxicity to hormesis. The debate on antibiotics' environmental fate is reinforced by the concern regarding induction/selection of microbial resistance and by the possible community alterations. Its aim being both to produce/validate tools for environmental monitoring (1,4) and to evaluate effects (2-3, 5-6), the ecotoxicological approach has been utilized for this hitherto little explored research field.

The goal to achieve a good status of water ecosystems according to the Water Framework Directive (WFD) 2000/60/EC, impose the implementation of reliable endpoints.
To assess river quality, the contemporary evaluation of water toxicity on *Daphnia* survival/reproduction and sediment status, such as benthic macro-invertebrates community structure (Tiber River), has been carried out: the integration of these two standard techniques proved a more reliable tool for further evaluation (4).
To tackle the alteration of the most important Mediterranean marine ecosystem (*Posidonia* meadows), the feasibility of phenol quantification coupled to 2-D electrophoretic protein analysis in rhizomes has proved a novel "diagnostic" tool for monitoring the health state of meadows (1). The identification of biochemical stress indicators in response to low environmental quality is still in progress, and they will be superimposed to the other analyses.

The widespread antibiotic use (in human/animal clinics and in agriculture) leads to the propagation of resistant variants in microbial communities. The phenomenon has been verified for bacterial communities in water and sediments of the Tiber where more than 80% of heterotrophic aerobic isolates were found to be resistant to different antibiotics. Multiresistance was also observed, and 5-antibiotic-resistant isolates were mainly found in sediments. The resistance pattern can be explained in term of use and persistence of the different antimicrobials (6).
To face this harmful kind of contamination, floating aquatic macrophytes (*Azolla filiculoides*, *Lemna minor* and *Pistia stratiotes*) were successfully tested as a decontamination tool for antimicrobial bioremediation (5).

Tetracyclines and sulphonamides enter terrestrial compartments due to the routine practice of organic fertilisation with contaminated liquid manure. They can be retained in soil and uptake by crop/weed plants has been demonstrated; the effect of such uptake is an hormetic response, according to the concentration in growth media (2).
Hormesis is an adaptive response characterized by a biphasic dose-dependent response, induced by exposure to a wide range of detrimental stimulations, and found in almost all biological systems. Hormetic response generally implies stimulation at low doses (typically a 30-60% higher than control) and inhibition at high doses; in particular, studies on the effect of antimicrobial drugs on growth rate demonstrated that hormesis is widespread, particularly in plants (from weeds, *Lythrum salicaria* to crop plants, *Zea mays*) (3).

GROUP LEADER Vittorio Colizzi ■ **STAFF SCIENTISTS** Maurizio Mattei • Maurizio Fraziano • Carla Montesano • Andrea Cabibbo ■ **POST-DOCS** Giulia Cappelli • Rosella Cicconi • Marilina Benedetta Santucci ■ **PHD STUDENT** Graziana Palmieri

Development of an anti-HIV neonatal vaccine based on a co-formulation of HIV-peptides and BCG

The project focuses on the design of a vaccine able to prevent HIV transmission from mother to child during breast feeding and/or to delay the appearance of the symptomatic AIDS.
The vaccine being developed consists of HIV peptides matching HLA genotypes of the Western Africa population and will be administered in association with BCG vaccine which acts as a strong adjuvant.
The critical issue was to identify HIV epitopes able to elicit a strong cellular and humoral immune responses in neonatal African populations.
Concerning the HLA alleles distribution in African population, our study confirms that several ethnic groups in Burkina Faso, Cameroon and Ivory Coast (Rimaibe, Fulani and Mossi) are significantly different from Northern and Eastern African Countries (3 ethnical groups from Sudan, Algerians). Hence, our design of the best HIV peptide vaccine takes this HLA allele distribution into consideration. The HIV-1 viral sequences for gag, nef, tat, vpr and vpu proteins in the study population has been sequenced.
In order to design this vaccine, the adjuvant properties of the tuberculosis BCG vaccination, widely administered to African neonates, was used to increase the immunogenicity of such HIV peptides. In first instance, HIV gag, tat, nef, vpr, vpu consensus sequences for the most prevalent HIV-1 clade present in Burkina Faso, Cameroun and Ivory Coast (recombinant clade A/G), were screened for HLA peptide-binding motifs, by using different available algorithms for prediction and scoring of each putative epitopes for all available HLA-class I and –class II alleles.
T cell epitopes used in this project have been selected by the "reverse immunogenetics" approach with three distinct criteria:
•selection of the cross-clade conserved regions of different HIV-proteins involved in CTL and helper response against HIV with particular attention to proteins involved in acute infection;
•identification of the promiscuous epitopes in the selected areas by using peptide-binding motifs analysis for HLA class I and II;
•selection of the minimum number of epitopes for each HIV protein that allow the response on any HLA haplotype and any virus clade.
All T-cell epitopes identified were synthesized and tested *in vitro* for their immunogenicity. The analysis was performed on African children and on age-matched Italian children.
Of particular interest was also the characterization of the innate and adaptive immune response of newborns from HIV+ mothers relevant to assess the ability of babies to respond to vaccination.
The project was accompanied by a program aimed at reducing mother-to-child transmission of HIV by counseling, HIV screening and introduction of a preventive administration of Nevirapine to HIV-positive pregnant women during labour, and to newborns within 72 hr of birth. Moreover, the introduction of HIV diagnosis by RT-PCR technique was of great help in the early identification of HIV-infected children.

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GROUP LEADER Vittorio Colizzi ■ **STAFF SCIENTISTS** Carla Montesano • Maurizio Fraziano • Andrea Cabibbo • Maurizio Mattei ■ **POST-DOC** Rosella Cicconi

Virologic and host factors determining HIV-progression in a paediatric cohort infected with a mono-phyletic HIV-strain

Colizzi V., De Oliveira T., Roberts R.J. 2007. Libya should stop denying scientific evidence on HIV. Nature 448, 992

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In 1998, outbreaks of human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) infection were reported in 418 children attending Al-Fateh Hospital in Benghazi, Libya. Six health care workers were accused of intentionally infecting these children with HIV-1 and were imprisoned, tortured and sentenced to death. Our involvement was aimed at understanding how the infection occurred and proving that the most reasonable explanation for HIV contamination was poor infection control practices, including the lack of sterile, disposable injecting equipment. Our efforts were also aimed at improving medical and laboratory practices at the hospital by participating in an Action plan from EU.

The molecular phylogenetic techniques analysis demonstrate that HIV-1 and HCV strains were already circulating and prevalent in this hospital and its environs before the arrival in March 1998 of the foreign medical staff. Epidemiological linkage of the HIV-1 and HCV clusters from Al-Fateh Hospital with sequences from sub-Saharan Africa is to be expected, given the large number of migrants within or passing through Libya. Virus sequences also contain temporal information about the date of origin and age of epidemics: The estimated date of the most common recent ancestor for each cluster pre-dated March 1998, sometimes by many years. The HIV-1 and HCV strains responsible were being spread and transmitted among individuals attending the hospital before March 1998, indicating that many of the transmissions giving rise to the infection clusters must have already occurred before the foreign medical staff arrived. Libya's Higher Judicial Council had commuted the death sentence to life imprisonment but failed to take into account convincing findings that the HIV infection was present in the hospital before the arrival of the health-care workers and ignored the concurrent outbreak of hepatitis C among the same population of children.

Susceptibility to HIV-1 infection, disease progression and clinical outcome is strongly influenced by differences observed in host genetic factors involved in HIV-1 cell entry, immune recognition and antigen presentation that may profoundly modify individual response to HIV-1 exposure, infection, pathogenesis and progression of HIV infection. Many studies have investigated the association of HLA variants with progression of HIV-infection. In this study we evaluated a defined study population from a restricted geographical area (Benghazi, Libya) and infected during the outbreak with the monophyletic strain of HIV. With this adding value in minimizing strain and other genetic background effects, and the limitation of the small subject group, we observed the key role of the HLA-B locus in HIV susceptibility, and the protective role of HLA-B58 supertype to HIV progression to AIDS. Actually, on the same pediatric cohort, we are evaluating other host genetic factors such as polymorphism of chemokines, their receptors and cytokines genes.

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The role of natural and microbial ligands in the activation of antimycobacterial innate immune response

The early steps of the interaction between *Mycobacterium tuberculosis* (MTB) and host cell are crucial for the outcome of infection. The evidence that immunocompetent individuals, who are exposed to MTB, can directly eliminate the pathogen without any sign of anti-mycobacterial adaptive immune response strongly suggests the presence of a protective innate immunity. In this context, the ability to control the enormous health burden of tuberculosis requires detailed understanding of the mechanisms that promote natural immunity to tuberculosis. In our studies, we have studied the molecular pathway through which TLR-9 stimulation by CpG oligodeoxynucleotides (ODN) induce antimycobacterial activity. Results showed that CpG ODN stimulation of monocytes induces intracellular mycobacterial killing by activating a Ca^{++} dependent phospholipase D which in turn promotes the maturation of MTB containing phagolysosomes. We have also identified a novel role played by two endogenous lysophospholipids, Sphingosine 1-phosphate (S1P) and Lysophosphatidic acid (LPA) in the activation of innate antimycobacterial response. Both lysophospholipids are able to induce intracellular mycobacterial killing in human macrophages and to activate a Ca^{2+}-dependent phospholipase D-mediated phagolysosome maturation. Moreover, S1P levels in airway surface fluid of tuberculosis (TB) patients are significantly less than those observed in non-TB control patients. Interestingly, the *in vitro* stimulation of Broncho-alveolar lavage cells coming from TB patients with either S1P or LPA significantly reduces intracellular growth of endogenous mycobacterial isolates. Finally, we have analyzed the role played by S1P in antigen presentation of monocytes and in the subsequent activation of *M. tuberculosis* (MTB)-specific CD4+ T cell response. Results show that S1P stimulation of MTB-infected monocytes promotes phagolysosome maturation and the transit of mycobacteria in MHC class II compartments and increases the frequency of MTB-specific CD4+ CD69+ T cells, expressing the inflammatory homing receptor CCR5. Taken as a whole, these results suggest that airway epithelial fluid associated S1P and/or LPA may play a protective role in the containment of intracellular mycobacterial growth, during the early steps of host-pathogen interaction, by activating antimicrobial and antigen processing and presenting activity of human macrophages, and that lysophospholipid modifications of pulmonary surfactant may negatively affect pulmonary anti-mycobacterial innate immunity and, hence, favor MTB replication.

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Development of animal models for biomedical research

Casetti R., Perretta G., Taglioni A., Mattei M., Colizzi V., Malkovsky M., Dieli F., Gianpiero D'Offizi and Fabrizio Poccia. 2005. Drug-induced expansion and differentiation of Vg9Vd2 T cells in vivo: the role of exogenous IL-2. J. Immunol. 175: 1593-1598.

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Animals models represent a fundamental tool to gain knowledge in the basic sciences, in the development of new drugs, in the discovery of new vaccines against tumours, infectious and parasitic diseases. Animals can be used to study systemic, organ specific, chronic or acute diseases, and can be divided into 4 classes: pretreated, selected, identified and genetically modified (OGM).
Since the quality of the animals represents a benchmark of good research all over the world, it is crucial to guarantee their standard qualit, through genetic, microbiological, biochemical and haematological controls.
In the animal facility of the University of Roma Tor Vergata, "Centro Servizi Interdipartimentale-STA", a large amount of knock-out and transgenic mice are employed in the selection of specific human diseases; outbred and inbred mice are currently bred for basic studies on vaccine development and autoimmune diseases. Experimental infections (e.g. *M. tuberculosis*, Influenza, HIV) are carried out by using a biosafety containment like a classical Trexler isolator; a specific program of animal welfare is also routinely carried out.
Knock-out and transgenic mice are employed for oncology studies, as in the development of a vaccine in the study of gene-specific inhibition of breast carcinoma in BALB-neuT mice, by active immunization with rat Neu or human ErB receptors; the monkey model (*M. fascicularis*) is a good model for investigating the drug-induced expansion and differentiation of Vgamma9Vdelta2 T cells *in vivo* under administration of exogenous cytokines; specific sensitized (TNP) CD1 mice are a classical model of Crohn's disease to investigate the role of T-lymphocytes interleukin-12 labeled, while BALB/c mice have been employed to study the immunogenicity of new formulation of interferon beta -1 for assessment of use in multiple sclerosis. A selected list of cell lines is being used to investigate the effect of new molecules in controlling the cell cycle and differentiation of cancer cells, while new medical apparatus is being tested on pig model.

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The Stress Response in Viral Infection and Cancer

The focus of our research is the understanding of the molecular mechanisms regulating the cellular stress response in viral infection and cancer.
We are interested in elucidating how viruses control the expression of cellular and viral genes by activating/inactivating stress-regulated cellular transcription factors, with the double objective of characterizing at the molecular level the pathogenetic events following the infection and to identify novel targets for antiviral chemotherapy.
A major field of interest of our laboratory is the comprehension of the functional role of the stress-regulated pro-inflammatory factor NF-κB in the control of viral infection and cancer cell survival. We investigate the mechanism by which RNA and DNA viruses activate NF-κB in human cells, and have recently demonstrated a relevant role of NF-κB in the pathogenesis of influenza and herpesvirus infections. We have shown that influenza A viruses activate the IKK/NF-κB pathway selectively in pulmonary cells, leading to massive IL-8 production and acute inflammation.
In the case of herpesviruses, we have identified the mechanism by which Herpes Simplex virus-1 utilizes NF-κB to enhance its replication, whereas a different member of this family, the oncogenic Kaposi sarcoma virus, enhances NF-κB-dependent MCP-1 expression in endothelial cells, stimulating angiogenesis during acute infection.
In addition to its role in inflammation and angiogenesis, NF-κB is involved in multiple aspects of oncogenesis, including virus-induced transformation and the control of apoptosis. NF-κB can suppress cell death pathways by switching on genes that dampen pro-apoptotic signals, including members of the Bcl-2 family, cIAPs, cFLIP and TNFR-associated factors. The anti-apoptotic role of NF-κB is particularly relevant in cancers presenting constitutive activation of the nuclear factor, an event triggered by either viral proteins or cellular enzyme dysfunction, leading to resistance to apoptosis induced by chemotherapy. Our lab has identified a group of natural compounds, the cyclopentenone prostanoids, which inhibit NF-κB by direct binding to the beta subunit of the IKK signalosome, and is investigating their anti-neoplastic activity in cancer cells characterized by aberrant regulation of the nuclear factor. We have now identified several natural and synthetic cyclopentenones as potent pro-apoptotic molecules in aggressive B-cell malignancies and in chemoresistant breast cancer.
We have also discovered a cross-talk between NF-κB and HSF1, the heat shock transcription factor responsible for the expression of cytoprotective heat shock proteins (HSPs) during stress. A fundamental role of HSF1 in human cervical carcinoma cell survival was recently demonstrated in our laboratory. We are now investigating the signaling pathway involved in the activation of HSF1 during viral infection, and are interested in elucidating the role of HSF1 and different HSPs in the control of viral mRNA expression and cell survival during infection with RNA viruses, including rhabdoviruses, paramyxoviruses and rotaviruses.

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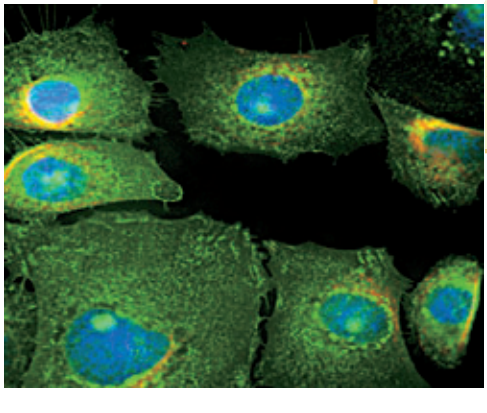
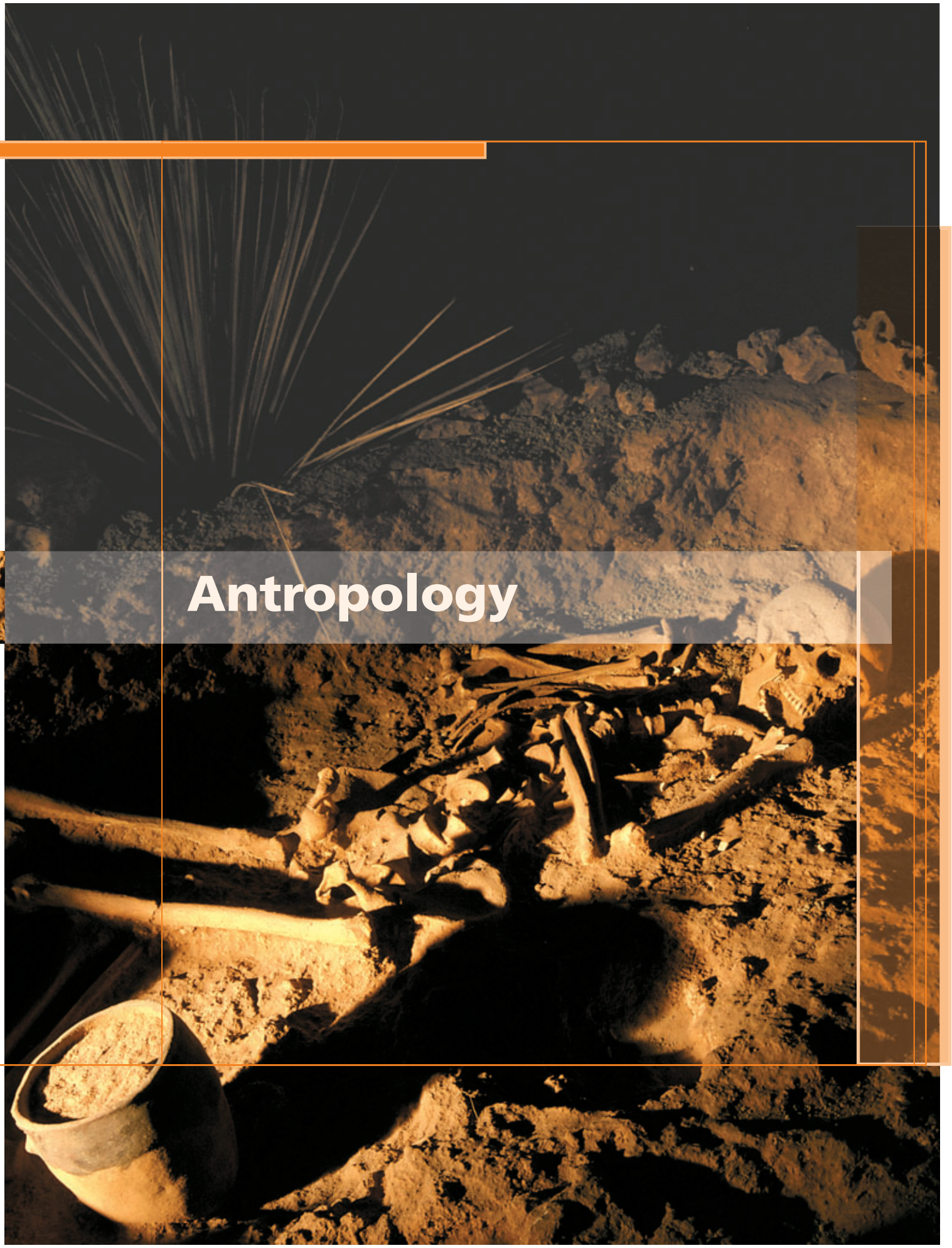


Chapter nine



Antropology

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Genetic adaptation and differential susceptibility towards environmental pathogenous factors

Giardina E., Pietrangeli I., Martínez-Labarga C., Martone C., De Angelis F., Spinella A., De Stefano G.F., Rickards O. and Novelli G. 2008. Haplotypes in SLC24A5 Gene as Ancestry Informative Markers in Different Populations. Current Genomics 9 (8).

Corbo R.M., Ulizzi L., Martínez-Labarga C., De Stefano G.F. and Scacchi R. 2007. Association of estrogen receptor alpha polymorphisms with fertility in populations with different reproductive strategies. Mol. Human Repr. 13(8): 537-540.

This research program comes under the field of scientific interest and activity that the Research Unit of Anthropology of Rome "Tor Vergata" developed for more than a decade in the framework of the study of the association between the anthropo-genetic variability of human populations and exogenous environmental factors involved in its origin and maintenance during time. Furthermore the scientific and experimental approach falls into the new main international research lines which have characterized Genetic Anthropology during recent decades. Special attention was devoted to problems concerning the impact of specific selective factors on the dynamic of molecular-genetic variability taking into account the genetic structure of some illiterate populations living in extreme environments, mainly the equatorial rain forest. In fact these populations are still considered as a uniquely useful model for clarifying open questions as to if, to which extent and how selective pressure due to environmental infection factors can impact on the genetic molecular variability of specific allelic variants associated with susceptibility to the environmental derived illnesses.

The following "niche" populations were taken into consideration: Cayapa and Colorado Indians living in an area of North-Western Ecuador known as hyper-endemic for infection by *Onchocerca volvulus*; a black population living in the same area and thus exposed to the same infectious disease. A panel of samples belonging to Central Africa endemic for the *O.volvulus* infection, has been also taken into account for comparison. Recently it has been reported that these Ecuadorian Black and Indian populations display diverse susceptibility to infection by *O. volvulus*. This diversity has been interpreted as a variability of the genetic variants at the level of codifying sites of HLA system (DRB1, DQB1, DQA1 and DPB1). This made it possible to hypothesize of a differential expression of the immune response against the infection. In order to test this hypothesis, 23 families belonging to the ethnic groups known as infected have been considered together with 12 individuals identified as potentially immunes. The experimental procedure included: the IEF characterization of GM and KM immunoproteins; the identification of HLA genotypes (DRB1, DQB1, DQA1 and DPB1 alleles), and the molecular typing of some HLA DQA1 and HLA DQB1 associated SNPs.

Moreover, the Cytochrome-P- 450-CYP1A1 and CYP2E1 genes have been recently hypothesized as associated with increased risk of lung cancer. Polymorphic variation of these genes has been also reported of this genes according to ethnic origin.

Thus, in this forthcoming step we intend to verify the extent of the described polymorphism in our population samples at the level of the CYP1A1 as well as CYP2E1. Results will be estimated in relation to the available epidemiological data on the lung cancer incidence among the populations taken into consideration.

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Glutathione S-transferases Theta and Mu as susceptibility markers in human population exposed to pollutants

Glutathione S-transferase is a superfamily of detoxification enzymes that play a central role in biotransformation of environmental pollutants and xenobiotic compounds. Various different classes can be identified due to their substrates and tissue specificity. GSTs genes are polymorphic. These genes can either have mutant alleles produced by a single mutation in the gene structure or they can be deleted. This deletion results in the presence or absence of the GSTT1 and GSTM1 genes and is coincident with the conjugator (GSTT1+ or GSTM1+) and non-conjugator (GSTT1-null or GSTM1-null) phenotypes respectively.
These polymorphisms are of particular interest as anthropogenetic and molecular markers in studies on intra- and inter-populations variability; and again as ecological/epidemiological markers to indicate genetic susceptibility. GST can play an important role in epidemiological studies: This is because the genetic polymorphism of these enzymes could identify subjects or groups of individuals more or less susceptible to pollutants. Therefore, this polymorphism is also useful in assessing different degrees of exposure and risk in order to show specific pathologies in different subjects.
The research project was launched to ascertain the possible correlation between the lack of detoxifing enzymes (GSTT1-null and GSTM1-null fenotypes) and asthmatic and allergic pathologies.
By using the PCR allele-specific technique we also aim to highlight the possible presence of a SNP in the third exon of the GSTT1 gene. This polymorphism is caused by a nucleotide substitution A→C (rs11550605) that leads to a change of the aminoacidic residue in position 104 (T104P). Due to this substitution, there is in fact a lack of the enzymatic activity.
As anthropogenetic markers we plan to evaluate the frequencies of null genotypes in different samples from European-origin populations and from African-origin populations. By comparing the frequencies obtained with those found in literature, we will be able to contribute to the geography of these markers.

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Fuciarelli M., Barone M., Piacentini S. and Porreca F. 2007. Relationship between human biomarkers and susceptibility to xenobiotics in workers exposed to pesticides. Advanced Studies in Biology.

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Tracing human migrations through molecular data

Rickards O., Martínez-Labarga C., Trucchi E., Renzi F., Casalotti R., Biondi G., Pepe G. and De Stefano G.F. 2005. Restriction fragment length polymorphisms of the type I collagen locus 2 (COL1A2) in two communities of African ancestry and other mixed populations of northwestern Ecuador. Human Biology, 77, 115-123.

Babalini C., Martínez-Labarga C., Giampaolo R., Tarsi T., Contini I., Barać L., Janićijević B., Martinović Klarić I., Peričić M., Sujoldžić A., Tolk H-V., Kivisild T., Villems R., Biondi G., Rudan P. and Rickards O. 2005. The genetic history of the Croatian linguistic minority of Molise (southern Italy): a maternal view. European Journal of Human Genetics, 13, 902-912.

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Tamm E., Kivisild T., Reidla M., Metspalu M., Glenn Smith D., Mulligan C.J., Bravi C.M., Rickards O., Martinez-Labarga C., Khusnutdinova E.K., Fedorova S.A., Golubenko M.V., Stepanov V.A., Gubina M.A., Zhadanov S.I., Ossipova L.P., Damba L., Voevoda M.I., Dipierri J.E., Villems R. and Malhi R.S. 2007. Beringian Standstill and spread of native American founders. PLoS ONE, 2(9): e829.

One of the major topics in Anthropology is to establish time and mode of evolution of human populations and to clarify some aspects of interest in their population history, their origin and their relationship with respect to each other. Several disciplines, in both historical and biological sciences, have investigated the past of our species addressing specific questions such as migration routes out of the African cradle towards the other continents.
During the last decades Molecular Anthropology has developed a wide range of approaches and methodologies in order to find suitable answers to these questions. Among the various molecules which could be used in unravelling human evolutionary history, mtDNA has been the molecule of choice because of its simple organization, maternal inheritance and relatively fast rate of evolution. The uniparental and clonal nature of mtDNA guarantees a direct transmission from mother to children without any shuffling of genes. Therefore, the variation between individuals is assumed to be the result of the mutations accumulated in maternal lineages, correlating to the different continents, starting from divergence from a common ancestor. For these reasons, mtDNA has proved to be useful in studying recent human evolution and in analyzing genetic affinities of populations from different geographical regions so as to delineate major expansions, dispersals and migrations of our species.
The aim of our research has focused on the phylogeographic analysis of mtDNA control-region and coding-region variations in different populations. In particular, the study of the geographic distribution and diversity of genetic variation has been used to reconstruct human expansion into the Mediterranean Basin, Africa and the Americas. Special attention has been devoted to ethno-linguistic minorities living in Italy, populations of Egypt, Ethiopia, Libya and Benin, and to autochthonous and mixed groups of Ecuador. The same populations have been studied for several nuclear DNA markers as well (COL1A2; CYP1A1; Immunoglobulin Enhancer HS1,2), including Y chromosome specific regions which represent the male counterpart to mtDNA studies.
These projects have been carried out in collaboration with several Italian and International research groups.

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Dietary variability and genetic origins of Ancient Human Populations: a combined ancient biomolecular approach

The aim of the proposed research is to reconstruct the genetic and demographic history and the diet of ancient individuals. This will be achieved through a multidisciplinary approach: ancient DNA analysis, i.e. phylogenetic reconstruction of mitochondrial DNA haplotypes, and stable isotope analysis, i.e. analysis of carbon and nitrogen stable isotope ratios in bone protein (collagen) extracted from ancient mineralised tissues (humans and the animals they may have consumed). Moreover, chemical analysis of teeth (through analysis of strontium isotope ratios) from selected individuals will allow to identify immigrants within the population.

Since both the extraction of DNA and collagen from archaeological bone and teeth require the destruction of the sample (up to 1 g for each analysis depending on the preservation), one of the main purposes of the proposed activity is to develop a single method to reliably extract DNA and bone protein (collagen) from minimal amounts of ancient mineralised tissues in order to provide both genetic and dietary information.

As archaeological specimens are rare and valuable, the development of a technique to obtain both genetic and dietary information from a single extraction, thus minimising destruction, is clearly desirable. In addition, such a method would also strengthen the case for obtaining permission to analyse specimens that have already been curated in museums.

Such an aspect is particularly relevant. In fact, whilst the methods of ancient DNA analysis and stable isotope analysis are well established for analysis of human remains from archaeological sites, up to now they have never been combined to study a single population. However this approach would allow dietary patterns to be examined in relation to ethnicity and recent migrations providing both cultural and genetic information. Issues involving subsistence, migration and genetic origins underpin important questions in prehistory.

The combined approach, which will be developed in the proposed research, can also provide an opportunity to assess the survival of DNA in relation to the organic preservation of bone and teeth samples (through collagen yield) in order to select samples with good DNA preservation, for subsequent ancient DNA analysis, by first conducting a less expensive and time consuming collagen determination.

This research has been carried out in collaboration with Italian and International research groups.

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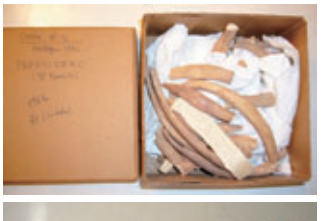

Appendix

Funding agencies

A.FA.R.
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ROMARK LABORATORIES
TAVOLA VALDESE
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Meeting Organization

LXVI Congresso dell'Unione Zoologica Italiana. Rome, September 19-22/2005 **(Chair: Prof. V. Sbordoni)**

100° Congresso Società Botanica Italiana. Rome, September 20-23/2005 **(Chair: Prof. A. Canini)**

Convegno "Ecosistemi naturali, qualità dei mieli e sviluppo", Villa Mondragone, Monte Porzio Catone (Rome), May 20/2006 **(Chair: Prof. A. Canini)**

5th International Conference on the Biology of Butterflies, Villa Mondragone, Monte Porzio Catone (Rome), July 2-7/2007 **(Chair: Prof. V. Sbordoni)**

Guest Scientists and Visiting Professors

Prof. Antonia Cattaneo
Département de Sciences Biologiques, Pavillon Marie-Victorin, Université de Montréal, Montréal, CANADA
Invited by Prof. Gianmaria Carchini

Prof. Micheal W. Parker
Biota Structural Biology Laboratory, St. Vincent's Institute of Medical Research,
Melbourne, AUSTRALIA
Invited by Prof. Mario Lo Bello

Prof. Penny E. Lovat
Dermatological Sciences School of Clinical & Laboratory Sciences, The Medical School, Newcastle University,
Newcastle upon Tyne, UK
Invited by Prof. Mauro Piacentini

Prof. Maryra Tejuca Martinez
Facultad de Biología, Universidad de la Habana, Centro de Estudio de Proteínas,
Habana, CUBA
Invited by Prof. Stefano Rufini

Prof. Matthew J. Picklo
Department of Pharmacology, Physiology, and Therapeutics UND School of Medicine,
Grand Forks, ND-USA
Invited by Prof. Patrizia Malaspina

Prof. Joel D. Richter
Department of Molecular Medicine, University of Massachussetts Medical School,
Worcester, MA-USA
Invited by Prof. Claudia Bagni

Prof. Zahra Zakeri
Biology Department, Queens College, City University of New York,
Flushing NY-USA
Invited by Prof. Mauro Piacentini

Prof. Lluis Quintana Murci
Visiting Professor
Département de Génomes et génétique, Institute Pasteur, Paris, FRANCE
Invited by Prof. Andrea Novelletto

Prof. Paul J. Dyson
Visiting Professor
Ecole polytechnique fédérale de Lausanne, Institut des sciences et ingénierie chimiques, BCH-LCOM,
Lausanne, SWITZERLAND
Invited by Prof. Mario Lo Bello

Prof. David Pauza
Institute of Human Virology, University of Maryland School of Medicine,
Baltimore, MD-USA
Invited by Prof. Vittorio Colizzi

Prof Boris Zhivotovsky
Institute of Environmental Medicine, Karolinska Institutet, Stockholm, SWEDEN
Invited by Prof. Mauro Piacentini

Prof. Michel Gibson
Department of Pathology, University of Pittsburgh School of Medicine,
Pittsburgh, PA-USA
Invited by Prof. Patrizia Malaspina

Prof Richard Roberts
New England Biolabs,
Ipswich, MA-USA
Invited by Prof. Vittorio Colizzi

Department Seminars

2005

February 1, 2005
Dr. Maria Victoria Schneider,
Institute of Biology Department of Animal Ecology University of Leiden, The Netherlands
"Evolution, Sex and Speciation"

February 10, 2005
Dr. Martin Wagner,
Department of Gastroenterology and Endocrinology, University Ulm, Germany
"Mouse models of pancreatic cancer"

March 3, 2005
Dr. Charlie Boone,
Banting and Best Department of Medical Research University of Toronto, Canada
"Chemical Genetics"

March 3, 2005
Dr. Sachdev Sidhu,
Department of Protein Engineering, Genentech Inc., South San Francisco, USA
"PDZ interactomics"

March 8, 2005
Dr. Pier Luigi Luisi,
Dipartimento di Biologia Università Roma3
"Dall'origine della vita alla biologia sintetica"

March 15, 2005
Dr. David J. Lipman,
Director NCBI, NLM, NIH Bethesda, USA
"Computing Discoveries in Biology"

April 13, 2005
Dr. Oliver Craig,
University of Newcastle-upon-Tyne Marie Curie Fellow – Università di Roma Tor Vergata
"The Recovery of Ancient Biomolecules to understand the Origins of Agriculture"

April 18, 2005
Dr. Elisabetta Visalberghi,
Istituto di Scienze e Tecnologie della Cognizione, CNR, Roma
"Uso di strumenti nel cebo dai cornetti. La soluzione di un mistero?"

April 29, 2005
Dr. Claes Andréasson,
Ludwig Institute for Cancer Research, Stockholm, Sweden
"A receptor-activated protease mobilizes two dormant transcription factors in yeast"

May 12, 2005
Prof. Joan S. Valentine,
Department of Chemistry and Biochemistry, University of California, Los Angeles, USA
"Protein misfolding or oxidative damage. What makes mutant copper-zinc superoxide dismutase toxic?"

May 31, 2005
Dr. Saverio Vicario,
Department of Biology, Yale University, New Haven, USA
"Codon usage through development: a comparative analysis in Drosophila melanogaster *and* D. pseudobscura*"*
July 6, 2005
Dr. Richard I. Morimoto,
John Evans Professor of Molecular Biology Director, Rice Institute for Biomedical Research Department of Biochemistry, Molecular Biology, and Cell Biology Northwestern University, Chicago, USA
"The stress of misfolded proteins in aging and neurodegenerative diseases"

September 5, 2005
Dr. Lars Kiemer,
Center for Biological Sequence Analysis, BioCentrum-DTU The Technical University of Denmark
"Wiring the human nucleolus"

September 5, 2005
Dr. Matthew J. Picklo,
Dept. of Pharmacology, Physiology, and Therapeutics UND School of Medicine, Grand Forks, USA
"Brain Metabolism of the Endogenous Neurotoxin 4-Hydroxy-2-Nonenal"

September 6, 2005
Prof. Michael W. Parker,
Associate Director and NHMRC Senior Principal Research Fellow Biota Structural Biology Laboratory St. Vincent's Institute of Medical Research Victoria, Australia
"Thanks for the memories: structure-based drug discovery"

October 3, 2005
Dr. Anna Di Rienzo,
Department of Human Genetics University of Chicago, USA
"Un modello evolutivo per le malattie comuni con dati di popolazione e studi di simulazione"

November 4, 2005
Prof. Joel D. Richter,
Program in Molecular Medicine, University of Massachusetts Medical School Worcester, USA
"Translational Control of the Cell Cycle and Cell Senescence"

November 28, 2005
Dr. Giuliano Elia,
Dept. für Chemie und Angewandte Biowissenschaften ETHZ Institut für Pharmazeutische Wissenschaften Zürich, Switzerland
"Proteomica in vivo ed ex-vivo per l'identificazione di nuovi targets in medicina molecolare"

2006

February 13, 2006
Dr. Marc Diederich,
Fondation Recherche sur le Cancer et les Maladies du Sang Laboratoire de Biologie Moleculaire et Cellulaire du Cancer Hopital Kirchberg- Luxembourg
"Effect of curcumin on the regulated expression of resistance genes in human leukemia"

February 23, 2006
Dr. Pier Giorgio Mastroberardino,
Pittsburgh Institute of Neurodegenerative Disorders University of Pittsburgh, USA
"Redox imbalance and early defects in neurodegenerative disorders"

March 27, 2006
Dr. Roberto Piva,
Department of Pathology and Center for Experimental Medicine (CeRMS), Laboratory of Molecular Oncology Università di Torino
"Dissecting the physiological and oncogenic signaling of Anaplastic Lymphoma Kinase"

April 4, 2006
Dr. Nurit Firon,
Department Plant Genetics, Institute Field and Garden Crops The Volcani Center, A. R. O. Bet Dagan, ISRAEL.
"The effect of extreme temperature conditions on pollen quality: biochemical and molecular aspects"

April 5, 2006
Dr. Martine Rahier,
Laboratory of Evolution and Entomology, Institute of Zoology, Faculty of Science, University of Neuchatel, Switzerland
"Alpine leaf beetle using plant toxins for defense: a free meal?"

June 15, 2006
Dr. Roberta Alfieri,
Dipartimento di Medicina Sperimentale Sezione di Patologia Molecolare ed Immunologia Università degli Studi di Parma
"Heat shock response to various stress factors: differences and similarities"

June 15, 2006
Dr. Michael Nevels,
Institut fuer Medizinische Mikrobiologie und Hygiene Universitaet Regensburg Forschungszentrum (FZL), Regensburg, Germany
"Innate and Epigenetic Control of Human Cytomegalovirus Infection"

June 22, 2006
Dr. Kris Gevaert,
Department of Medical Protein Research, Proteome Analysis and Bioinformatics Unit Flanders Interuniversit Institute for Biotechnology Ghent University
"Diverse applications of diagonal reverse-phase chromatography (COFRADIC) in the field of proteomics"

October 16, 2006
Dr. Mario Gimona,
Marie Curie Unit of Actin Cytoskeleton Regulation Negrisud Institute,Santa Maria Imbaro (Chieti)
"Protein linguistic approaches for the functional analysis of modular protein domains"

October 17, 2006
Prof. Dr. Joachim Burger,
Institut fur Anthropologie AG Palaeogenetik Johannes Gutenberg – Universitat Mainz, Germany
"The first European farmers, their cattle and what DNA from bone can tell us about"

October 18, 2006
Dr. Giuseppe Longobardi,
Università di Trieste
"A History and Geography of Human Syntax?"

November 14, 2006
Dr. Alex Sigal,
Department of Molecular Cell Biology, The Weizmann Institute of Science Rehovot, Israel
"Variability and memory in protein levels in human cells"

November 28, 2006
Dr. Stuart Calderwood,
Director of Division of Molecular and Cellular Biology Department of Radiation Oncology, BIDMC, Harvard Medical School, Boston, USA
"Heat Shock Factor 1 in tumor progression"

December 13, 2006
Dr. Antonella Farsetti,
Dipartimento di Oncologia Sperimentale, Centro Ricerca Sperimentale - Istituto Regina Elena e INMM, Consiglio Nazionale delle Ricerche Roma
"Profilo trascrizionale e pathway molecolari a valenza prognostica nel cancro della prostata"

2007

January 25, 2007
Dr. Lluis Quintana Murci,
Unit of Molecular Prevention and Therapy of Human Diseases, Institut Pasteur, Paris France
"Human Genome Diversity: Population Genomics and Infectious Disease"

March 15, 2007
Dr. Dominik Gront,
Laboratory of Theory of Biopolymers, Faculty of Chemistry UW Warszawa, Poland
"Protein structure modeling in a reduced conformational space"

March 29, 2007
Dr. Des R. Richardson,
Professor of Pathology and National Health and Medical Research Council of Australia Principal Research Fellow
"Nitric oxide and its interaction with GSH and iron in macrophages"

April 4, 2007
Dr. John E. Eriksson,
Department of Biology Åbo Akademi University Turku, Finland
"Signaling networks switching between survival and cell death"

April 11, 2007
Dr. Daniela Barilà,
IRCCS Fondazione S. Lucia, Roma
"Ruolo delle chinasi nel controllo dell'apoptosi e nello sviluppo dei tumori"

April 12, 2007
Dr. Frederick L. Coolidge,
Psichology Department University of Colorado at Colorado Springs, USA
"Genetic influences on personality disorders: gender identity disorders and frontal lobe dysfunction in childhood and adolescence"

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Dr. My Hedhammar,
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"Investigation of the fibre formation of a miniature spider protein: implications for the development of a novel functionalised bioma"

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Dr. Jiri Neuzil,
Apoptosis Research Group, School of Medical Science, Griffith University, Southport, Australia
"Molecular mechanism of apoptosis induced by "mitocans" epitomises multiple role of reactive oxygen species and Bcl-2 family proteins at mitochondrial level"

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Dr. Gianluca Cestra,
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"Regulation of Tyrosine Kinase Receptor Endocytosis"

May 31, 2007
Dr. Tommaso Villa,
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"Quality control of RNA processing: identification of a novel splicing fidelity factor"

July 3, 2007
Dr. Herman Favoreel,
Department of Virology, Parasitology, and Immunology Faculty of Veterinary Medicine Ghent University, Belgium
"Herpesvirus interactions with signaling pathways that result in morphological and cytoskeletal alterations"

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Director of the Laboratory of Organometallic and Medicinal Chemistry, Ecole Polytechnique Fédérale de Lausanne, Switzerland.
"Metal-based drugs that overcome GST resistance"

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"Degradazione di mRNA neuronali e plasticità sinaptica"

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"Il ruolo della sintesi proteica nello sviluppo dello scompenso cardiaco"

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High-throughput exploration of functional residues in protein structures

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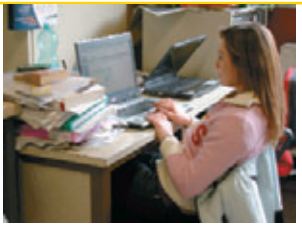

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Nucleotide post-transcriptional modifications of BC1 non-coding RNA during brain development: new insights into the BC1-FMRP complex

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Role of ATM in Fas-induced apoptosis in lymphoid cells

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Identification of activating and repressing elements on Apaf1 promoter gene

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Ruolo della proteina reticulone-1C (RTN-1C) nella modulazione del processo apoptotico e sue implicazioni in patologie degenerative'

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Superossido Dismutasi a Cu,Zn nella funzionalità mitocondriale e citoscheletrica: importanza nel mantenimento dell'omeostasi in cellule di origine neuronale

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Phylogeography and conservation genetics ao Parnassius mnemosyne L. 1758 (Lepidoterapia, papilionidae)

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Genetic characterisation of the italian endemic genus SALAMANDRINA (Fitzinger, 1826) (Amphibia: salamandridae)

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New insights into fish growth parameters estimation by means of length-based methods

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Effects of a small headwater dam on macroinvertebrate communities and environmental variables in a Mediterranean stream

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Nutrients and fish effects on plankton community in freshwater mesocosms

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A polyphasic approach to the study of EPS-producing heterocystous cyanobacteria from biofilms in Roman hypogean monuments

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Structure and function of benthic microbial community in highly variable freshwater systems

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Filogeografia del Parnassius apollo Linnaeus, 1758 (Lepidoptera, Papilionidae)

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Origine, variabilità e struttura genetica delle popolazioni italiane di Hystrix cristata.

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Popolamento umano del Sahara libico durante l'olocene. Analisi molecolare delle linee materne in popolazioni antiche ed attuali del Fezzan
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Ampliamento delle basi conoscitive per la messa a punto di tecnologie per il controllo della biologia riproduttiva del tonno rosso in acquacoltura

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(Theses 2005-2007)

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Gene expression profiling of Mycobacterium tuberculosis and human macrophages during host-pathogen interaction

Marilina Benedetta Santucci
Ruolo della sfingosina1-fosfato nella risposta immunitaria all'infezione da Mycobacterium Tuberculosis

Massimo Amicosante
Functional immunogenetic of Berylliosis: from susceptibility marchers to model of specific immunotherapy

Nunzia Sanarico
The effect of IL-2 in the immunology of human monocyte-derived dendritic cell: a new tool for the in vitro generation of antigen presenting cells with an implemented ability in priming Th1 immune response

Paolo De Vito
Relazione tra PH intracellulare e produzione di specie reattive dell'ossigeno nella risposta immune e innata: ruolo dello scambiatore sodio/idrogeno e del peptide natriuretico atriale

Carla Montesano
Analysis of CD8+ T lymphocytes during Structured and Partial Therapy Interruption of Highly Active Antiretroviral Therapy in HIV-infected adult and pediatric patients

Luigia Pace
IL-4-induced protection of CD4+ CD25- Th cells from CD4+ CD25+ regulatory T cell-mediated suppression

Giulia Zanin
Studio del danno e della riparazione del dna in cellule umane e marine di soggetti giovani e vecchi

Fabiola D'Aquilio
Activatory properties of lysophosphatidic acid (LPA) on human THP-1 monocytes

Graziana Palmieri
Studio preclinico nel modello murino e nel primate non umano per lo sviluppo di un vaccino pediatrico contro la trasmissione verticale di HIV/AIDS

Chiara Focaccetti
Inibizione immunologica del processo di cancerogenesi nei tumori della mammella insorti in topi BALB/C transgenici per il prodotto dell'oncogene ERBB/NEU mediante immunoterapia attiva

Viviana Speranza
Costruzione di un BCG ricombinante che esprime antigeni di MTB e valutazione della sua immunogenicitÃ in vivo.

Emanuela Valente
Monociti e terapia HAART in pazienti HIV+

Chiara Agrati
Attività antivirale dei linfociti T gamma-delta

Alessia Anselmi
Dinamica virale e risposta immune HIV-1-specifica in neonati sottoposti a terapia antiretrovirale ed immunoricostituzione in bambini infettati da HIV-1 con differente risposta virologica alla terapia

Publications (2005-2007)

Amici C., Rossi A., Costanzo A., Ciafrè S., Marinari B., Balsamo M., Levrero M. and Santoro M.G. 2006. Herpes Simplex virus disrupts NF-kB regulation by blocking its recruitment on the IkBa promoter and directing the factor on viral genes. J. Biol. Chem. 281, 7110-7117.

Agrati C., Martini F., Nisii C., Oliva A., D'Offizi G., Narciso P., Nardacci R., Piacentini, M., Dieli F., Pucillo L.P., and Poccia F. (2005). CD1d expression by hepatocytes is a main restriction element for intrahepatic T-cell recognition. J Biol Regul Homeost Agents, 19(1-2), 41-8.

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Albertano P. (2006). Biotecnologie per la diagnosi e il controllo del danno prodotto da biofilms epilitici. In: C. Sabbioni F. Persia, L. Castelletti, (eds.), Biologia e Archeobiologia nei beni culturali: conoscenza, problematiche e casi di studio, pp. 112- 124, AIAR e Musei Civici- Comune di Como, Como.

Albertano P. (2006). I procarioti. In: Edizione Italiana del Mauseth, Botanica, vol 2., pp. 107-135, Idelson Gnocchi, Napoli.

Albertano P., Bruno L., and Bellezza S. (2005). New strategy for the monitoring and control of cyanobacterial films on valuable lithic faces. Plant Biosystems 139: 311-322.

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