CENTRE SCIENTIFIQUE DE MONACO

HSH the Sovereign Prince Albert II surrounded by Prs D. Allemand and P. Rampal

CENTRE SCIENTIFIQUE DE MONACO

Founded in 1960 by Prince Rainier III, the Monaco Scientific Centre (CSM) is now a world-renowned centre for scientific research. Working under Professor Patrick Rampal, CSM's president, Scientific Director Professor Denis Allemand strives to maintain multidisciplinary excellence in the realm of Biology, Environmental management and Health.

THE MONACO SCIENTIFIC CENTRE

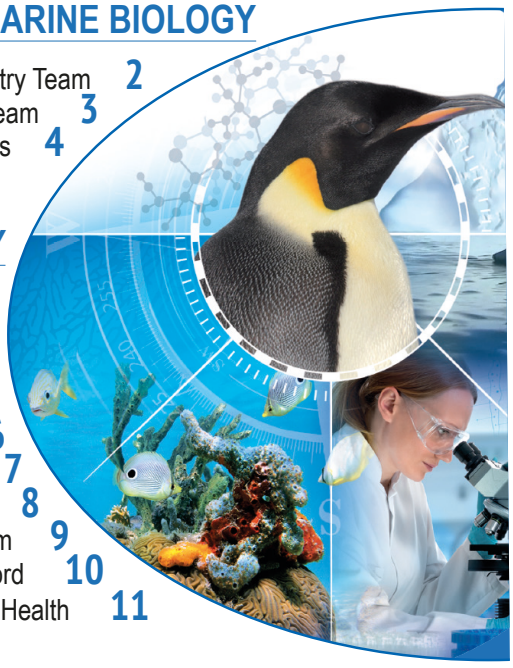
THREE RESEARCH DEPARTMENTS

Long recognised for its high quality work in the field of Marine Biology, early research at the Monaco Scientific Centre focused on coral ecosystems and coral physiology, both excellent indicators of the state of health of the oceans. Two further departments have been added to this pioneering unit at the request of HSH Prince Albert II : one specialising in Polar Biology in 2010 and another in Medical Biology in 2013.

The Polar Biology Department studies the behaviour, physiology and ability of certain species of penguins in the South Pole to adapt to environmental change. Just like coral reefs, the Antarctic ice sheet is an excellent indicator of the state of the planet's health and the impact of environmental change.

The Medical Biology Department cary out both fundamental and applied research in the fields of cancer, muscular dystrophy and digestive ecosystems, ensuring the data is rapidly shared with clinical practice in the Principality. Other research themes are explored as part of international programmes like Monacord, a Eurocord project, which runs the International Sickle Cell Disease Observatory to study patients suffering from this condition. This department also includes a World Health Organization Collaborating Centre for Health and Sustainable Development and a funding agency for Clinical Research in the Principality.

Summary



"The aim of our mission is to build bridges between these three disciplines to advance research."

Pr Patrick Rampal

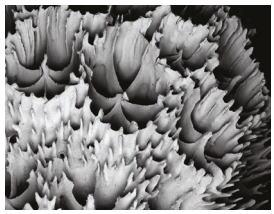
CORAL PHYSIOLOGY AND BIOCHEMISTRY TEAM

Research theme

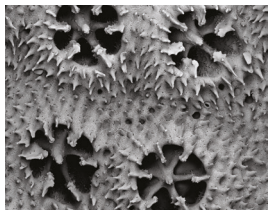
The main research theme of the Physiology and Biochemistry team is the study of biomineralisation in corals; the process underlying the formation of the coral skeleton. Our research addresses three major questions:

- A physiological question: what are the mechanisms involved in the control of biomineralisation?
- An evolutionary question: does the biomineralisation process require the development of a specific set of biological tools and/or does it utilize ancestral characteristics shared between distantly related organisms?
- An environmental question: how and why do corals respond to climate change and why are certain coral species more resistant than others?

Skeleton of *Stylophora pistillata*



Detail of skeleton of *S. pistillata*



Detail of skeleton of *S. pistillata*

Biological models studied

Our main models are the tropical reef-building coral, *Stylophora pistillata* and the Mediterranean Red Coral, *Corallium rubrum*, on which we have conducted research for over 30 years. These corals belong to the subclasses Hexacorallia and Octocorallia respectively, two groups that acquired the ability to biomineralise independently in their evolutionary history. Among the Hexacorallia, we also study other symbiotic (*Acropora sp.*, *Pocillopora sp.*) and non-symbiotic (*Tubastrea sp.*) corals. Our comparative studies concern a range of biological organisation, from the scale of whole organisms to the scale of genes, via tissues, cells and molecules.

Coral *Corallium rubrum*

Coral *Stylophora pistillata*

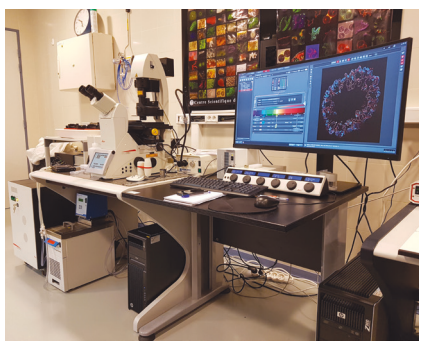
Coral *Tubastrea sp.*

Techniques used

Most of our experiments are conducted in the laboratory under controlled conditions utilizing a wide range of complementary techniques:

- Physiology: isotopic kinetics, pharmacology, microelectrodes *in-vivo*.
- Optical and electronic microscopy for ultrastructural studies.
- *In-vivo* cell imaging including confocal microscopy.
- Biochemistry, molecular biology, bioinformatics and genomics.

In vivo microelectrodes



Confocal microscope

Our collaborations

We work in collaboration with:

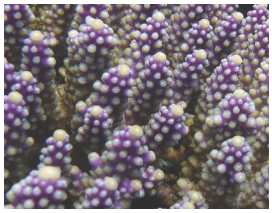
- The other teams at the CSM,
- International teams (e.g. France, Italy, Germany, United Kingdom, Saudi Arabia, USA).

CORAL ECOPHYSIOLOGY AND ECOLOGY TEAM

The research undertaken by the Ecophysiology and Ecology team focuses on the interactions between corals, their associated microorganisms and the surrounding environment. We primarily investigate the effects of climate change, pollution and nutrient availability on coral health and growth. Our research contributes to a better understanding of the functioning of coral reefs and is particularly useful for organizations dedicated to the conservation and restoration of coral reefs.

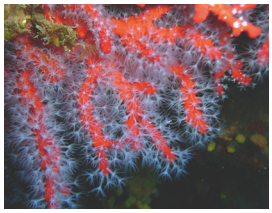
Study models

We mostly study reef-building corals from the tropics and the Mediterranean Sea, and have recently also added the red coral, gorgonians, soft corals as well as cold-water and deep sea corals to our model species.



Tropical coral *Acropora sp.*

Mediterranean coral *Cladocora caespitosa*



Red coral *Corallium rubrum*

Deep coral *Dendrophyllia ramea*

Gorgon *Paramuricea clavata*

Soft coral *Xenia sp.*

Research axis

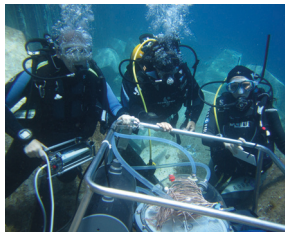
We use these different coral models to study:

- The effects of environmental changes (e.g. temperature, acidification, pollution).
- The contribution of various nutrients and trace elements to the health and growth of corals.
- The benefits of the symbioses between corals and microorganisms.

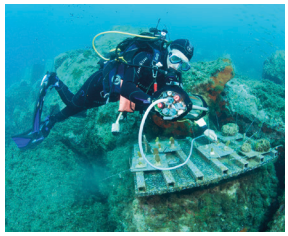
Techniques used

We conduct both field experiments to study corals in their natural environment and laboratory experiments under controlled conditions. To better understand the coral ecophysiology, we use a range of different techniques: stable isotopes, PAM fluorometry, biochemical and enzymatic analyses as well as microbiology and molecular biology techniques and bioinformatics to study the coral's microbial partners.

Drilling of a coral colony



Respirometry machine



PAM (Pulse Amplitude Modulation) fluorimetry

Our collaborations

- We work with many laboratories to further our research. In addition to collaborations with the other teams at the CSM, we collaborate closely with several external laboratories:
- Regionally with the International Agency for Atomic Energy and the Institut de la Mer de Villefranche,
- Internationally with laboratories in Italy, Spain, Denmark, United Kingdom, Israel, Saudi Arabia, Australia, USA.

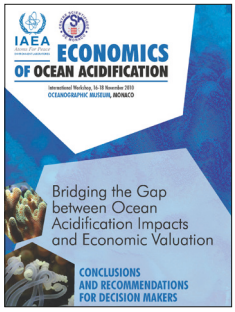
ENVIRONMENTAL ECONOMICS

The Environmental Economics section focuses on three themes:

Socio-economic impacts of climate change and of ocean acidification

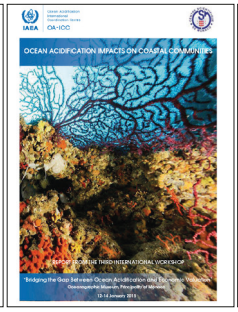
The United Nations Sustainable Development Goals (SDGs) have replaced the Millennium Development Goals (MDGs) for the period 2016-2030. The COP21 and SDG 13 (on climate change) highlight the need to accelerate the economy decarbonization and the worldwide reduction of CO_2 emissions, and to strengthen the international community's commitment to take collective measures to drastically reduce CO_2 emissions. The CSM's environmental economics theme studies the socio-economic impacts generated by CO_2 emissions due to climate change or to ocean acidification. This is also reflected in the series of Workshops "Bridging the gap between ocean acidification impacts and economic valuation" jointly organized by the CSM and the IAEA under the leadership of Dr Hilmi.

Brochures from Workhops organized by the Environmental Economy

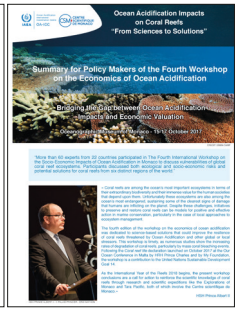


2010

2012

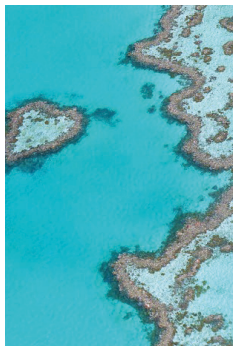


2015



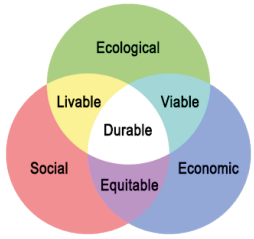
2017

Assessment and enhancement of coral reefs



In tropical environments, particular attention has been paid to studying coral reef assessment methods. Collaboration with experts in the social sciences has made it possible to take into account economic as well as social and cultural aspects in an ecosystem approach. Several SDGs are concerned by the coral reefs' health (food security, poverty alleviation, human health…). In addition, governance aspects are crucial when talking about the management of natural capital and the conservation of environmental resources. Indeed, there are many actors involved in the process of protection or resilience. Thus, the decision is taken at different levels ranging from local to global by a multitude of actors. Communication is essential for research to reach all levels of decision-making.

Economic policies and sustainable development



When we talk about environmental policies, the notion of sustainable development is essential because it includes the three pillars: economic, social and environmental. Environmental policies are a component of broader economic policies and, without an understanding of the macroeconomic and social context in which countries find themselves, it is impossible to make adequate policy recommendations.
In a world marked by local and global fragilities and instabilities of all kinds (political, social, economic and financial), an environmental catastrophe can have particularly devastating effects on the economy and the human-being. Through a macroeconomic approach, the "Environmental Economics" theme can address the major global issues and give them the necessary political and international dimension to make them intelligible by political decision-makers.

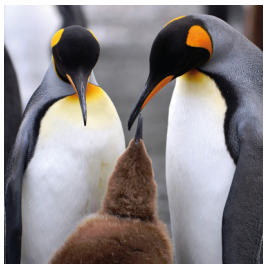
ECOLOGY AND EVOLUTION TEAM

The main objective of the research carried out within the Department of Polar Biology is to understand the evolution of polar ecosystems, the most vulnerable regions of our planet today hit hard by climate change. We are interested in seabirds and especially penguins because they are valuable bio-indicators of the health of their ecosystems, and therefore incomparable biological models to study the health of our planet.

Main study species

Our research mainly focuses on 3 species of penguins (king, Adélie, emperor penguins) located on 4 sites (sub-Antarctic archipelagos of Crozet and Kerguelen, Adélie Land and Dronning Maud Land on the Antarctic continent).

Emperor penguin



King penguin

Adélie penguin

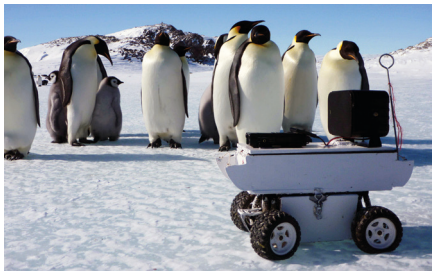
Research axes

We aim to assess the adaptive capacities of penguins to environmental changes through:

1. the study of individual responses to these changes,
2. the projection of the evolution of these populations according to the projected scenarios of climate change,
3. the development of non-intrusive observational methodologies in natural environments.

Technological innovations

We use many innovative technologies to minimize the impact of our observations on the study species, e.g. automatic identification and weighing systems, camera tracking and recording of activities of individuals in the colony. Today, we can also access information previously impossible to obtain thanks to rovers introduced inside the colony, or miniaturized bio-loggers (GPS, Argos, Temperature-Depth recorders, or accelerometers) to track penguins while foraging at sea. To manage and analyze the huge amount of data we use artificial intelligence and machine-learning techniques.



Rover in a colony of penguins

Gateway identification / automatic weighing

Life observatories

In partnership with the CNRS and the programs of the French (IPEV) and German (AWI) Polar Institutes, our Department implements long-term monitoring of undisturbed penguin populations. The implantation of electronic tags (0.8 g) under penguins' skin, allows the tracking of these birds thanks to detection antennas deployed on the pathways to their breeding colony.

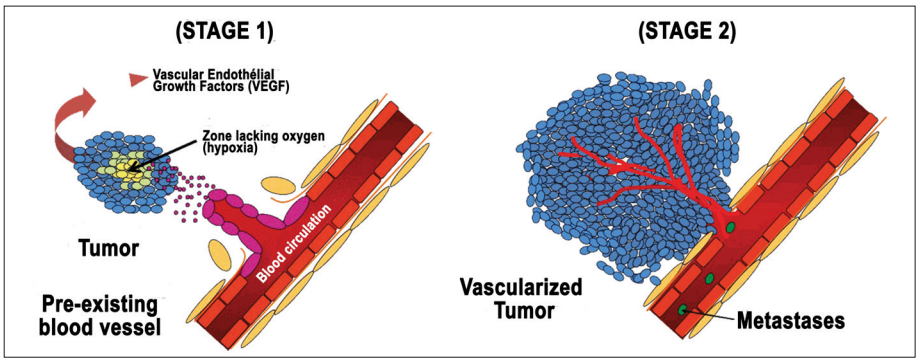
With more than 17,000 penguins marked and monitored continuously since 1998, this exceptional database allows us to study the impact of environmental variability on populations and their fate, and to define crucial areas for penguins, which are essential to preserve as Marine Protected Areas.

MECHANISMS OF RESISTANCE TO TARGETED THERAPIES TEAM

Advances in oncology over the last 20 years have doubled the cure rate of this disease to reach 40-50% globally. Different strategies have led to remarkable therapeutic advances including:

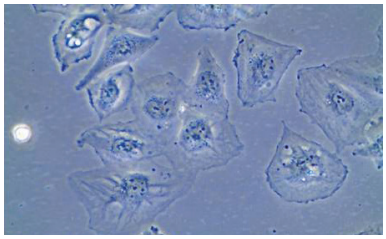
1. targeting specific genetic mutations;
2. inhibition tumor vascularization;
3. reactivation of the patient's antitumor immune system.

Despite these encouraging results, many patients do not respond to these treatments and certain cancers remain incurable, especially in the metastatic phase. Understanding the mechanisms that allow tumors to escape current therapies is therefore essential.



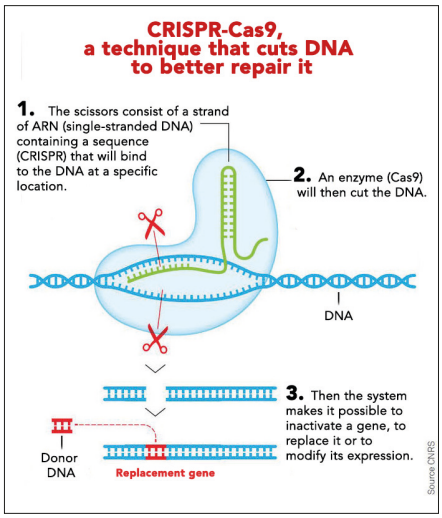
Neoangiogenesis is the mechanism for creating new blood vessels, in order to nourish cancerous tumors and ensure their growth

Our research programs aim to study the development of resistance to treatments by tumor cells with a focus on kidney and breast cancer in adults and the brain cancers in children. Numerous strategies are dedicated to identification of the processes responsible for the evolution of a localized cancer, stemming from a not very aggressive state to a disseminated and incurable tumors. These factors make it possible to anticipate relapses and thus optimize treatment strategies. Additionally, these factors could also serve as relevant therapeutic targets.

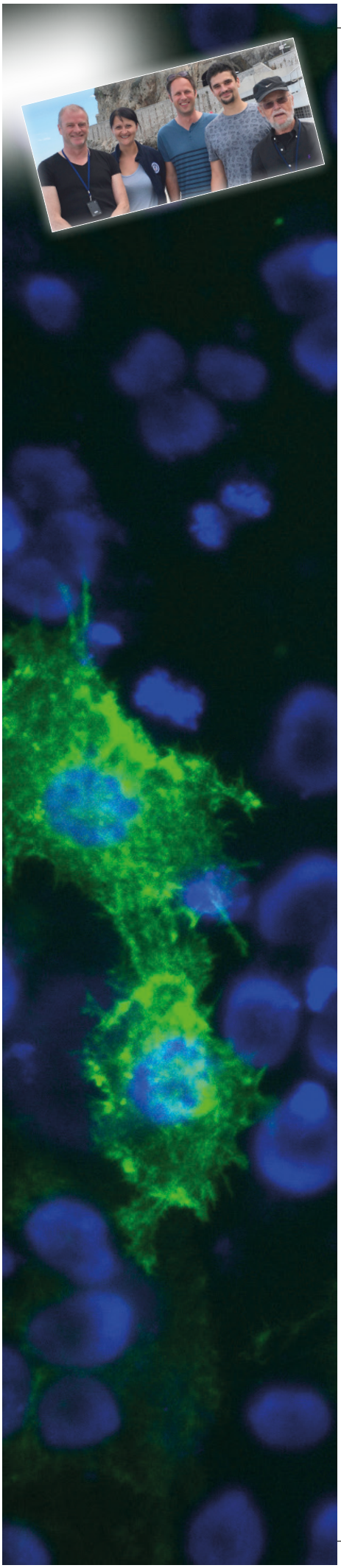


Cancerous cells of the child's brain (medulloblastomas) in 2D culture

These ambitious research programs require knowledge and specialized equipment to discover new therapeutic targets and test innovative treatments. Our research uses elaborated techniques such as "CRISPR-Cas9" to allow the inactivation of genes implicated in cancer development in laboratory cellular models.

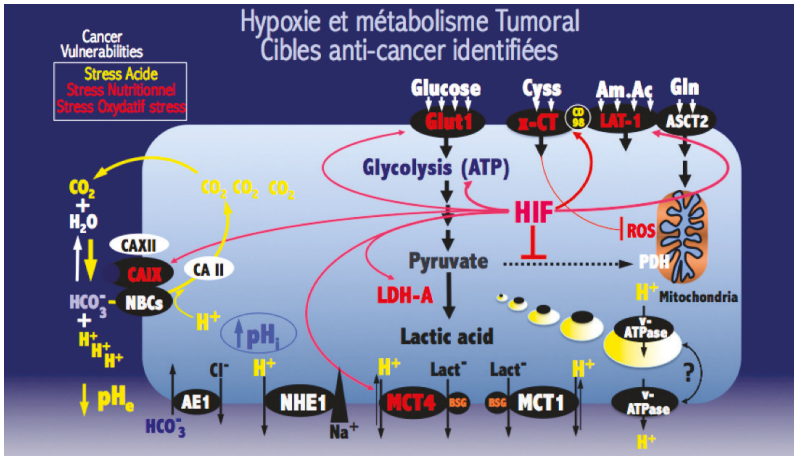


Our projects involve close collaborations with the surgical and pathology departments of several hospitals such as the Princess Grace Hospital, the CHU and the Antoine Lacassagne Centre in Nice along with the Curie Institute in Paris. Creation of this "virtuous circle" of researchers/clinicians will contribute to a better knowledge of the mechanisms involved in adult and pediatric cancers. Through this, the research developed at the Monaco Scientific Centre will refine precision medicine by considering that each patient is a unique case to be cared for in a personalized way.



TUMOR HYPOXIA AND METABOLISM TEAM

The Tumor Hypoxia and Metabolism team is developing a physiological approach to the study of tumor cells utilizing genetics (CRISPR-Cas9 gene disruption) for the identification and validation of new and previously unexplored targets with anti-cancer potential.
We are currently studying hypoxic, nutritional, acid and oxidative stresses in fast-growing tumors. Unlike normal cells, these tumor cells, which are often poorly vascularized, are able to exploit a cellular physiology in an "extreme milieu" to survive and develop in an acidic tumor environment, which is scarce in glucose, amino acids and oxygen. These "borderline" environmental conditions thus select the emergence of metastatic, multi-resistant and aggressive clones (altered bioenergetic metabolism, exacerbated macro-autophagy and micro-pinocytosis).



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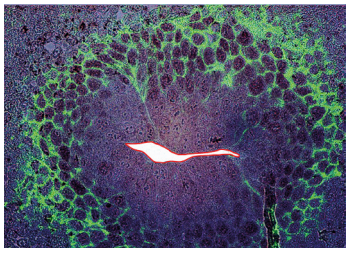
Major actors in the regulation of intracellular pH (pHi) and amino acid transport

Acid stress from aerobic respiration

The exploration of intracellular pH regulators, including carbonic anhydrases CA9, CA12 and CA2, Na^+/H^+ exchangers and bicarbonate transporters, has highlighted the major acidifying role of carbon dioxide (CO_2) from aerobic respiration. Blocking these pH regulators inhibits tumor growth. This research is continuing in the context of acidic stress to further understand the influence on cellular signalling pathways and the induction of immunological tolerance mechanisms with respect to tumors.



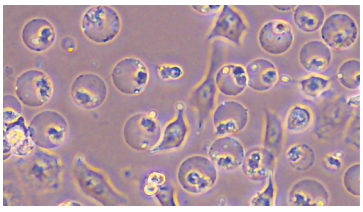
Cross section of a blood vessel feeding a tumor showing the green hypoxic zone

Acid stress resulting from fermentative metabolism (Warburg effect)

Inhibition of lactic acid export by genetic invalidation or pharmacology of monocarboxylate transporters (MCT1 and MCT4) has shown a major role of intracellular acidosis in stopping tumor growth. This research has also revealed that slowing tumor acidosis' reactivates the immune system against the tumor.

Nutritional stress: two transporters of essential amino acids (LAT1) and glutamine (ASCT2)

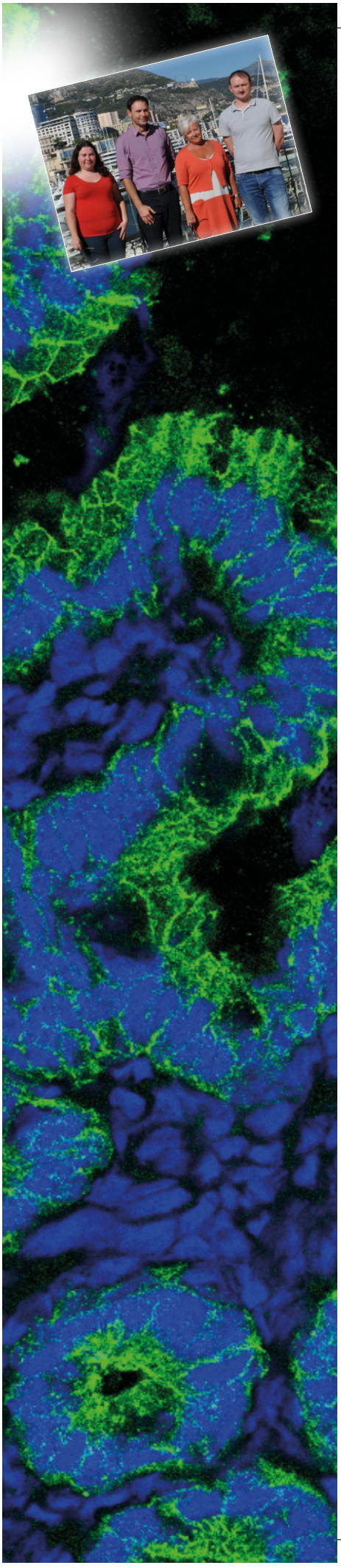
The team also explores mechanisms to "starve" tumor cells by genetic invalidation (by CRISPR-Cas9) or pharmacological inhibition of amino acid transporters that are abnormally overexpressed in tumor cells.



Cell death by ferroptosis

Oxidative stress and the cystine transporter xCT

This transporter is fundamental for the synthesis of the major antioxidant of the cell, glutathione. Its invalidation unveiled the existence of an oxidative mechanism of rapid cell death termed "ferroptosis". Our research exploits this cell death mechanism to eradicate cancers resistant to targeted therapeutics.

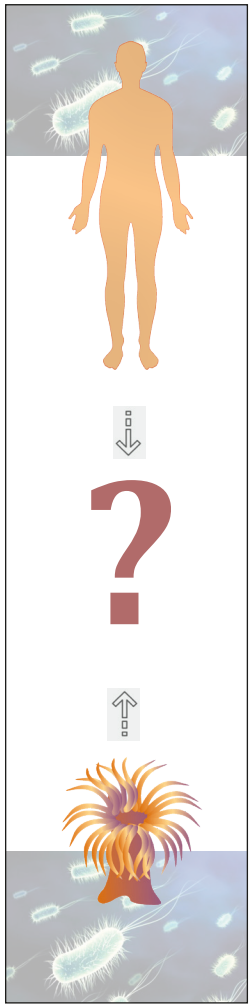


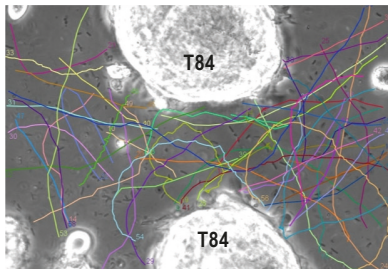
ECOSYSTEMS AND IMMUNITY TEAM

Increasing resistance to antibiotics constitutes a pressing problem in human health and push researchers to find new strategies to fight against infectious diseases.
In addition, climate change causes oceans to warm up and acidify but also promotes the emergence of new pathogens for corals as well as humans.
The research of the Ecosystems and Immunity team at the Monaco Scientific Centre focuses on the interactions between host and pathogens in diverse models in order to define new strategies towards fighting infections and preventing the development of new bacterial diseases.

Immune response host/bacteria in vertebrates

The gastro-intestinal microbiota a.k.a "microflora" is an extremely complex ecosystem that coexists in equilibrium with the host. When this equilibrium is disturbed, for example through dysbiosis due to antibiotic treatment, more serious health issues can arise such as infections, ulcers, inflammatory disease of the intestines, irritation of the colon and sometimes cancer. Otherwise, the microbiota play a crucial role in the efficacy of the immune system which has "learned" to differentiate between good and bad bacteria. One of the strategies to fight infections consists in better understanding the immune response of the host in charge of getting rid of the invading pathogenic bacteria. We study how the immune system within the digestive track recognizes non-pathogenic (commensal) bacteria from the pathogenic ones.

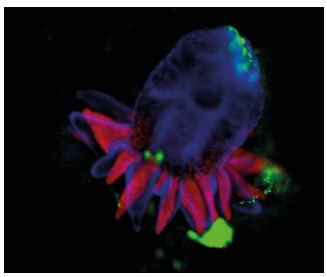




Trajectories of bacteria in search of their targets (human T84 cells)

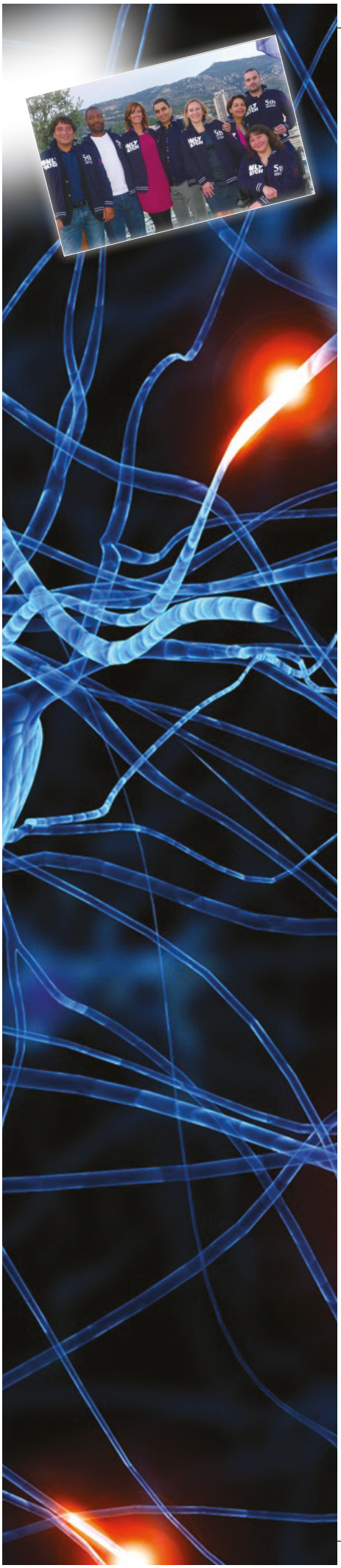
An emerging model to study innate immunity, the sea anemone

Today, we know that cnidarians have their own microbiota and that certain pathogenic bacteria can cause corals to bleach. We use the sea anemone, *Aiptasia pallida* as a model to better understand the relationship between the host animal and the pathogens. To do so, studying the sea anemone seems very relevant as sequencing projects recently revealed that the innate immune system of the anemone holds many similarities to vertebrate's including human's. *Aiptasia pallida* is therefore a choice organism to improve our knowledge of the relationship between cnidarians and bacteria within the context of coral ecology and also to discover antibiotic strategies that could help human health. Our interdisciplinary research has the potential to help us understand the defense response of the anemone against marine pathogens capable of infecting humans, and also to apprehend certain coral pathologies of bacterial origin.

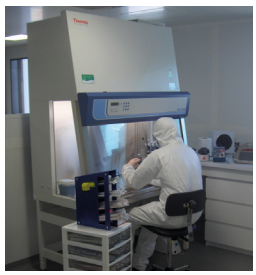


Sea anemone (blue), symbionts (red) and bacteria (green)

Results form these studies could then translate into outcomes for environmental management strategies for coral reefs as well as in biomedical applications to fight pathologies caused by infections of the gastro-intestinal track in humans.



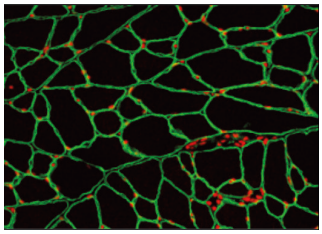
BIOTHERAPIES APPLIED TO NEUROMUSCULAR DISORDERS TEAM



The International Associated Laboratory, Biotherapies Applied to Neuromuscular Disorders, brings together teams from the Monaco Scientific Centre and the University of Versailles-Saint-Quentin-en-Yvelines. It develops research programs dedicated to the design and development of new therapeutic approaches based on gene transfer methods and/or modulation of messenger RNA splicing. These approaches are intended to treat genetic diseases, particularly those affecting the neuromuscular system.

Innovative biotherapies for neuromuscular diseases

Neuromuscular diseases of genetic origin are defined by a lack of muscle control or destruction of muscle tissue. The most emblematic of these, Duchenne muscular dystrophy (DMD), is caused by mutations that affect the gene encoding dystrophin, a protein essential for an effective function of muscle cells.



Cross section of healthy skeletal muscle showing the location of dystrophin (red) around muscle fibers (green)

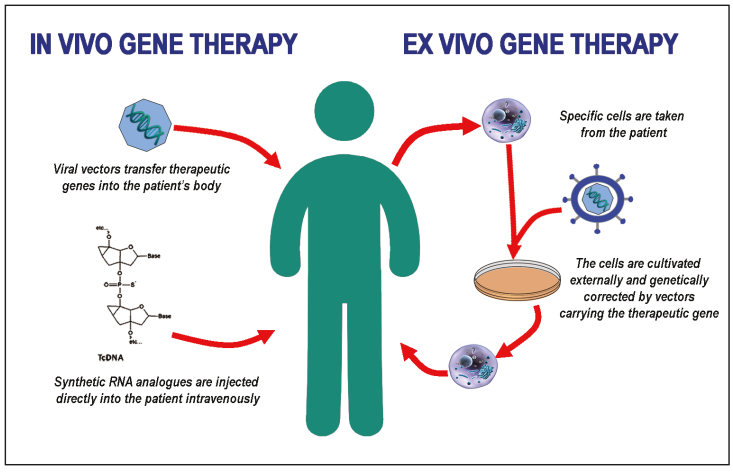
This particularly severe and very disabling myopathy still does not receive any satisfactory treatment. Recent advances in the field of biotechnology have recently opened up the prospect of new specific “RNA surgery” or genomic editing therapies to restore the production of normal proteins.

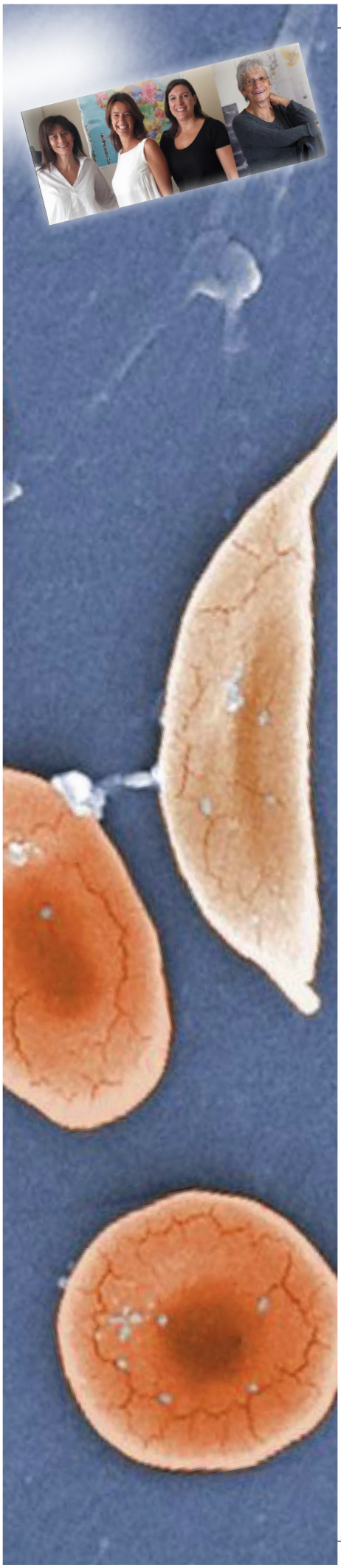
Tricyclo-DNA, a new generation of synthetic nucleotide analogs for splicing modulation approaches

Regarding exon-skipping RNA surgery, we have demonstrated the superiority of a new type of synthetic nucleotide analog, tricyclo-DNA (ASO-tcDNA). After intravenous administration, they are distributed effectively to the entire skeletal musculature. The team demonstrated a restoration of dystrophin in DMD mouse models, treated with these tcDNA, as well as a significant improvement in muscle, respiratory, cardiac and cognitive functions. All these results demonstrate the therapeutic potential of this generation of molecules that we plan to evaluate soon in DMD patients.

Design of a gene transfer platform

AAV viral vectors have a high potential for gene transfer into the neuromuscular system. In this field, our team works on the development of new technologies to produce these vectors compatible with large scale manufacturing processes.

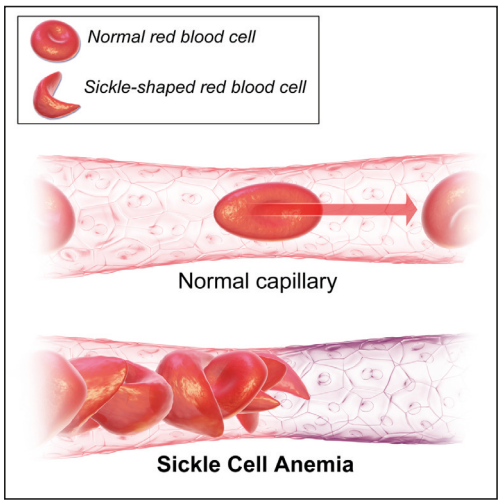




MONACORD

Thanks to the support of H.S.H. Prince Albert II and in collaboration with the Government of the Monaco's Principality, in 2012 the association Monacord, "International Sickle Cell Disease Observatory", was created thanks to an agreement between the Monaco Scientific Centre and Eurocord-Paris.

Sickle Cell Disease is a life-threatening, hereditary disease which involves the hemoglobin, which mainly affects people from sub-Saharan African regions. Because of the recent global migration of the population, Sickle Cell Disease now affects many patients worldwide, with more than 50,000 patients in Europe.
Sickle Cell patients have symptoms such as anemia, vaso-occlusive crisis and cerebral vascular accidents that cause poor quality of life and limited life expectancy. The only definitive cure is the hematopoietic stem cell transplantation.



Eurocord has obtained considerable international recognitions within its scientific studies based in particular on:

- stem cell transplantations from HLA-identical siblings as a definitive curative treatment of sickle cell disease,
- the development of transplantations from non-HLA-identical donors,
- new treatments for pregnant women suffering from sickle cell disease,
- umbilical cord blood banks for sickle cell families.

In his future projects, Monacord will take care of:

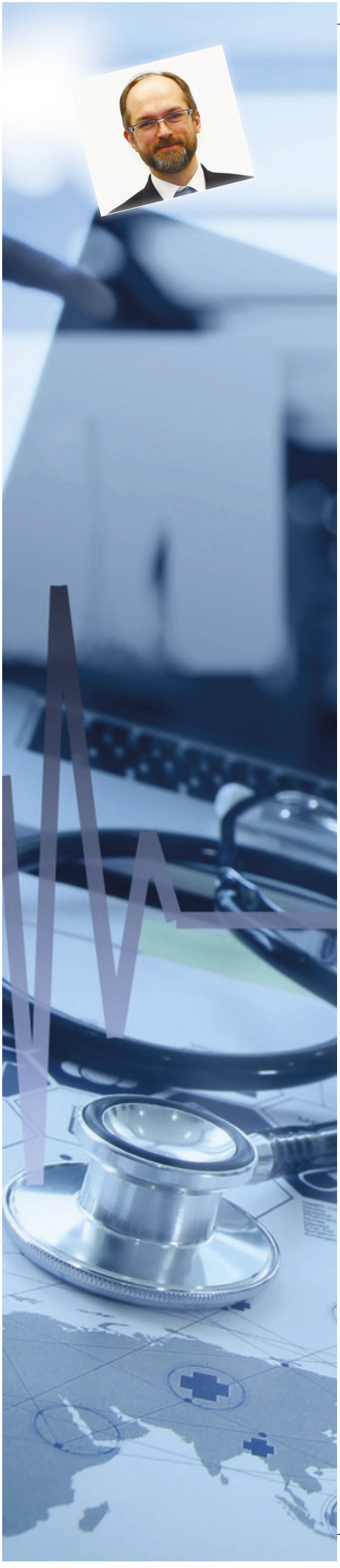
- formulation of clinical recommendations for the management of sickle cell disease including indications for hematopoietic stem cell transplantation or other innovative therapies such as gene therapy,
- development and coordination of actions for the diagnosis and treatment of sickle cell disease,
- dissemination of knowledge on this subject, particularly in African countries,
- identification of centres for the development of therapeutic clinical trials suitable for local resources,
- implementation of cost-effectiveness studies and optimization of treatment, based on the new resources of the countries.

To achieve its objectives, Monacord works closely with:

- Eurocord, Saint-Louis Hospital, Paris (France).
- International registries: EBMT (European Bone Marrow Transplant Group), CIBMTR (Center for International Blood and Marrow Transplant Research), NIH (National Institute of Health).
- Bambino Gesù Hospital, Rome, Vatican, Italy.
- University of São Paulo, Brazil.
- Cordon de Vie, Scientific Association of the Principality of Monaco.
- Department of International Cooperation, Principality of Monaco.
- Muhimbili University of Health and Allied Science, Tanzania (MUHAS)...

MONACORD

eurocord



HUMAN HEALTH

To fulfill the new mission entrusted to the CSM by H.S.H. Prince Albert II, one of the chosen axes was to stimulate and promote clinical research in the Principality. The Human Health Unit of the CSM is essentially devoted to this axis since its creation in 2009.

Its activity consists essentially of an annual call for projects which aims to finance clinical research projects taking place in the health institutions of the Principality of Monaco, with the objectives defined as follows:

- Support and boost Monegasque clinical research to promote medical progress.
- Participate in improving the quality of care by evaluating new diagnostic and therapeutic methods.
- Scientifically validate new medical knowledge.
- Promote collaborations between health professionals and between health institutions.

The calls for projects concern all areas of clinical research. Projects may include therapeutic assessment, technology and innovation evaluation, prevention, diagnostic strategies, quality of care, risk analysis, in all medical or surgical disciplines. However, priority is given to projects dealing with aging and/or cancer.
The Monaco Scientific Centre provides methodological and regulatory support to the project leaders, assists the teams in the implementation of their projects and regularly monitors their progress, both scientifically and on the use of the sums allocated.

Since 2009, this activity has attracted sustained interest from the Monegasque medical community and has funded 38 research projects. It has also enabled the establishment of partnerships of excellence in collaborative projects with other institutions (Paoli Calmette Institute, University Affiliated Hospital) and research institutions (CNRS, INSERM).

The activities of the team were completed in 2012 by another component, labeled “Health - Climate - Environment”, which focuses on the effects of environmental changes on human health. It is not, strictly speaking, a research activity but rather activities of teaching, training and scientific communication such as an online course on the health consequences of climate change. They are structured aroung partnerships in the Principality of Monaco (Prince Albert II Foundation, Department of Education) or abroad (e.g. World Health Organization, Institut Pasteur).

These activities are now more formally integrated into the team’s activities since its designation as the WHO Collaborating Center for Health and Sustainable Development in 2016.

ASSOCIATION OF THE FRIENDS OF THE MONACO SCIENTIFIC CENTRE

My intention is to provide a new dynamic for the Scientific Centre. I wish to complement the research activity performed in the context of the marine environment with the development of biomedical and polar research programs. These multidisciplinary scientific programs will bring together talent and strongly consolidate a single reality: that the Principality of Monaco is oriented for excellence in the future.

Extract from the speech of H.S.H. Prince Albert II during the inauguration of the new laboratories of the CSM on October 1, 2013.

This non-profit Monegasque association has two major objectives:

- To develop the knowledge and the scientific culture in the Principality by the diffusion, with our members, of information on the activities of the Monaco Scientific Centre, by the setting up of conferences general public, debates or visits of scientific sites,
- Assist the Monaco Scientific Centre in developing its scientific activities through financial support in addition to State grants for research programs, teaching programs or study grants for doctoral or post-doctoral students.

To achieve these goals, we need you to develop our actions.

Support our projects and make a donation!

CENTRE SCIENTIFIQUE DE MONACO

ASSOCIATION DES AMIS DU CENTRE SCIENTIFIQUE DE MONACO

Gouvernement Princier
PRINCIPAUTÉ DE MONACO

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