Managing Sustainability?
Proceedings of the 12th Management International Conference
Portorož, Slovenia, 23–26 November 2011

CODI-STRAT - AN INTERDISCIPLINARY NETWORK GEARED TOWARDS SUSTAINABLE MANAGEMENT OF CHRONIC AND INFECTIVE DISEASES

Sodin-Semrl S.[1,2], Lakota K. [1,2], Dubuisson J.[3], Ellul B.[4], Fenech A.[4], Ceron Madrigal J.[5], Thallinger G.[6], Perretti M.[7], d'Acquisto F.[7], Raynes J.[8], Romero F.[9], Filipovic N.[10], Chetrit Russi C.[11], Veranic P.[12], Caldin M.[13] Rozman D.[14], Mulvey M.[15]and Tomsic M.[2]

[1]University of Primorska, Faculty of Mathematics, Natural Sciences and Information Technology (FAMNIT), 6000 Koper, Slovenia (ssodin1@yahoo.com)

[2]University Medical Center Ljubljana, Rheumatology, Vodnikova 62, Slovenia and Institute of Rheumatology, Slovenia (matija.tomsic@guest.arnes.si)

[3] Centre National de la Recherche Scientifique (CNRS), Center for Infection and Immunity of Lille, France (jean.dubuisson@ibl.fr)

[4] Universita ta Malta, Pathology Department, Faculty of Medicine and Surgery, Malta (bridget.ellul@um.edu.mt ; anthony.fenech@um.edu.mt)

[5] Universidad de Murcia, Department of Animal Medicine and Surgery, Spain (jjceron@um.es)

[6] Technische Universitat Graz, Institute for Genomics and Bioinformatics, Austria (Gerhard.Thallinger@tugraz.at)

[7] Queen Mary and Westfield College, University of London, William Harvey Research Institute, UK (m.perretti@qmul.ac.uk ; f.dacquisto@qmul.ac.uk)

[8] London School of Hygiene and Tropical Medicine, Department of Infectious and Tropical Diseases, UK (John.Raynes@lshtm.ac.uk)

[9] Instituto Biomar S.A., Leon, Spain (microleon@institutobiomar.com)

[10] Bled School of Management (IEDC), Bled, Slovenia (Nenad.Filipovic@iedc.si)

[11] Bioiberica S.A., Barcelona, Spain (cchetrit@bioiberica.com)

[12] University of Ljubljana, Faculty of Medicine, Institute of Cell Biology, Slovenia (peter.veranic@mf.uni-lj.si)

[13] San Marco Veterinary Laboratory (SMVL), Padova, Italy (mc@sanmarcovet.it)

[14] University of Ljubljana, Faculty of Medicine, Center for Functional Genomics and Biochips, Institute of Biochemistry, Slovenia (damjana.rozman@mf.uni-lj.si)

[15] University of Utah, Department of Pathology, Division of Microbiology and Immunology, Salt Lake City, USA (mulvey@path.utah.edu)

ABSTRACT

A collaborative effort of clinicians, infectologists, molecular biologists, pharmacologists, veterinarians, bioinformaticians, management and education specialists is united in order to develop novel strategies of detecting early stages of chronic and infective diseases, their prevention and therapy. CODI-STRAT integrates 15 centers conducting leading–edge research of chronic inflammatory/infective diseases from seven European (five Mediterranean) countries and the USA, with specific aims to: i) establish long-standing partner center cross-disciplinary collaborations for clinical studies and research, ii) provide young investigators with broad and content-driven training and employability and iii) promote scientists up-skilled in genomics, transcriptomics, tissue expression, human serological and genetic studies, bioinformatics, chip technology, cell cultures and animal models, all directed toward clinical translation and chronic/infective disease management. This manuscript outlines the goals, partner roles and development of CODI-STRAT and its programme.

Keywords: Prevention/treatment strategies, management of chronic/infective diseases**,** inflammation/infection, multicenter/multidisciplinary consortium

INTRODUCTION

CODI-STRAT consortium is an international, multicenter, interdisciplinary network of research, clinical and education centers formed in order to provide advancement of knowledge and innovation in anti-inflammatory/anti-infective strategies. The network bridges interdisciplinary partners with the major aims to detect chronic diseases at earlier stages, identify optimal markers, monitor, and treat chronic diseases with innovative therapies. This platform will be supplemented with molecular, cellular, serological, immunological, biopharmaceutical technologies, as well as FACS, microarrays, qPCR, bioinformatics and mathematical modeling. High-quality non-scientific training will complement the research portfolio with management, patent issues, entrepreneurial skills and strategic planning for industrial collaborations.

Background

The world's elderly population, more prone to chronic disease, is growing. The result is a quiet epidemic of chronic illness that causes 86 % of deaths in Europe (WHO press release EURO/05/06, Copenhagen, 2006), which could largely be preventable (Figure 1).

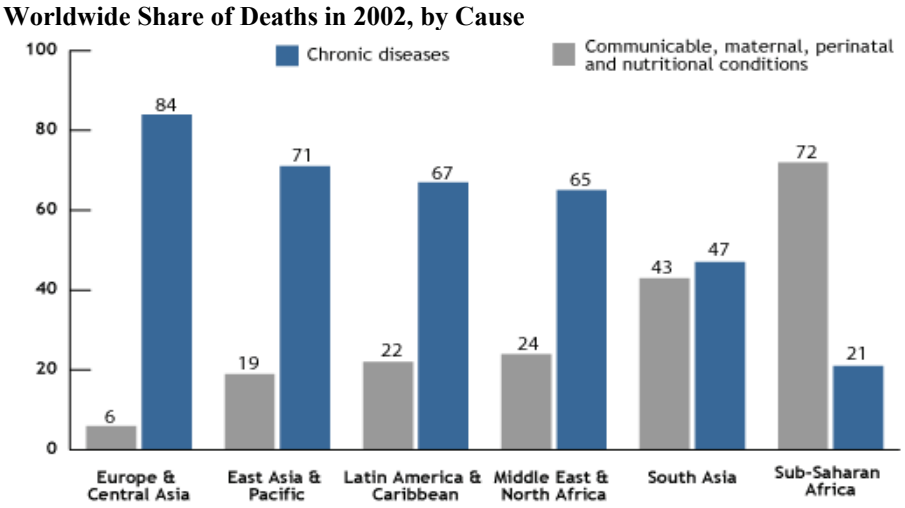

Figure 1: Colin D. Mathers et al., "The Global Burden of Disease in 2002: Data Sources, Methods, and Results," GPE Discussion Paper 54 (Geneva: World Health Organization, 2003), available at www.who.int/evidence .

Chronic inflammation represents the underlying cause and driving force for the development and exacerbation of the majority of chronic diseases (Weiss U., 2008), such as rheumatoid arthritis (RA), asthma and persistent viral/bacterial infections leading to great economic (worldwide average: 3% of gross domestic product) and social burden. In developing countries the economic impact is additionally greater because many people with chronic illnesses are of working age.

In addition, many approved anti-inflammatory drugs, such as leflunomide, methotrexate, non-steroidal anti-inflammatory drugs, biologicals and clinical trials of novel potential anti-inflammatory therapies have shown a variety of undesirable side-effects (e.g. patients prone to infections). More financial and human resources are urgently needed to optimize treatments and detection methods that could greatly benefit a wide range of diseases and improve patient health. In the past few decades the drive towards new therapies for chronic diseases has strongly increased in the U.S., as compared to Europe. This is currently changing and thus there will be a demand for well-trained clinicians, immunologists, molecular and cellular biologists, pharmacologists, veterinarians, bioinformaticians and management specialists in the chronic anti-inflammatory and anti-infective fields.

The mission/vision of the network is the long-term collaboration of a trans-Mediterranean, European, as well as international network for first-rate research and training of young investigators in the advancement of chronic disease knowledge, innovation and prevention, while providing a base for efficient, mutually beneficial collaborations and enabling expedited knowledge, information, technology and reagent transfer. Overcoming difficulties in data interpretation, wasteful duplication and competition, while increasing productivity, is a priority of the network. A computer and information technology support system is planned for the science, training and transfer of knowledge activities.

General Outline of CODI-STRAT

Studies have recently reported the necessity for early detection/diagnosis leading to better prognosis and outcome of chronic inflammatory diseases (Medzhitov R., 2008; Galli S.J. *et al.,* 2008). Infections can cause and/or lead to the exacerbation of chronic inflammatory conditions, while on the other hand, chronic inflammatory diseases can also lead to the susceptibility of the organism to infections. Both infectious diseases and inflammation share common cellular/molecular/biochemical pathways. One of these pathways involves acute phase reactants in mammals.

Major acute phase proteins can represent excellent tools for early inflammatory disease detection, diagnosis, progression determination and outcome. Serum amyloid A (SAA), as one of the two major acute phase proteins in humans, can be elevated up to 1000-fold during inflammation and can represent a key driving force during the longitudinal progression of disease and tissue remodelling. SAA is not only an early and sensitive marker of

inflammation, tissue trauma and infection, it is also an excellent clinical biomarker (Malle E. and F.C. de Beer, 1996; Cunnane G. *et al.,* 2000), following disease activity and, in a number of pathologies, can predict mortality (Morrow D.A. *et al.,* 2000). SAA is especially implicated in chronic inflammatory diseases, such as rheumatoid arthritis (RA), atherosclerosis, cardiovascular diseases and cancers (Lakota K. *et al.,* 2010). SAA is considered a better predictor of clinical progression and outcome than CRP in RA (Cunnane G. *et al.,* 2000) and is a predictive and prognostic marker of certain cardiovascular diseases and cancers (Katayama T. *et al.,* 2005; Morrow D.A. *et al.,* 2000; Johnson B.D. *et al.,* 2004; Malle E. *et al.,* 2009).

SAA at physiological concentrations is further known to be an active participant in homeostasis, endowed with beneficial properties in protection against viral and bacterial infections (Lavie M. *et al.,* 2006; Shah C. *et al.,* 2006; Hari-Dass R. *et al.,* 2005) and is necessary in host defense. On the other hand, sustained SAA levels occur during chronic inflammation and promote tissue degradation (Sodin-Semrl S. *et al.,* 2004) (Figure 2).

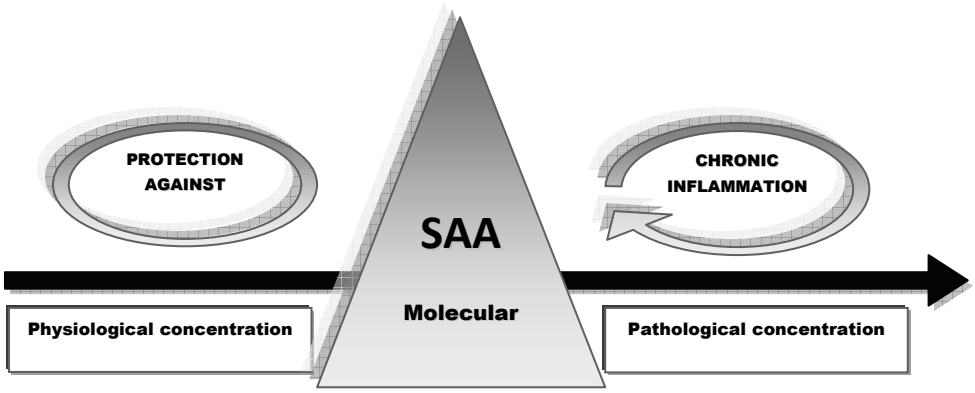

Figure 2: A critical event in the inflammatory process is activation of "para-inflammatory" transitional phase leading to chronic signaling, which, if unregulated, can result in persistent stimulation of pro-inflammatory mediators. Some acute phase reactants, such as Serum amyloid A (SAA) act as a molecular switch in the early regulation of inflammation. Among the objectives of CODI-STRAT are the development of strategies that would identify early inflammatory molecules needed to be targeted, as well as test existing and novel anti-inflammatory mediators.

As an acute-phase protein, SAA acts similarly in humans and mice, making mice models accessible. This has not been the case with the classical inflammatory marker, C-reactive protein (CRP). In certain autoimmune diseases, such as systemic lupus erythematosus, ulcerative colitis, CRP does not show elevated levels, during an obvious presence of

inflammation (Wettero J., 2008; Sjowall C., 2007), so SAA can represent the more optimal inflammatory biochemical marker. In children's infections (such as measles, varicella, rubella, mumps, echo-30 meningitis, chronic hepatitis B and C, and in some Kawasaki cases), 56% of patients had raised SAA concentrations while CRP was not increased above normal levels (Miwata H. *et al.,* 1993). However, CRP is still routinely used as the only routine biochemical marker of inflammation.

In comparison with human studies, the veterinary science, as evident at the last International meeting on acute-phase proteins in Helsinki 2010 and also from recent publications (Eckersall P.D. and R. Bell, 2010) has already identified, recognized and used SAA as a standard non-specific marker of disease, disease activity and outcome, making SAA a protein with huge commercial potential. There is considerable evidence that SAA has a protective role against infection for instance when SAA is made in large amounts in milk following inflammatory stimuli in many animals, such as cows and swine (Molenaar A.J. *et al.,* 2009; de Jesus Rodriguez B. *et al.,* 2009). SAA itself is however, relatively easily degraded and if the protein is to be used in a therapeutic way to help control infection then it is important to understand which regions of the protein need to be retained and others that can be changed to increase stability or bioavailability. CODI-STRAT proposes that development of reagents, detection kits, and a deeper understanding of acute phase reactants, e.g. SAA and its biology will generate technology to measure SAA more reliably, for instance through measurements of a specific isoform or epitope; generating know-how which will impact the development of novel anti-inflammatory and anti-infective drugs. These efforts/approaches will help to clarify the biological roles associated with this acute-phase reactant. So, we deem timely to investigate the properties of SAA, providing standard detection of SAA in diseases and enabling development of therapies based on its functions.

Brief overview of work programme and objectives

The strength of this network is the integration of core basic research with high-throughput techniques, bioinformatic analyses and biopharmaceutical compounds coupled with cellular, animal and human serological studies. The scientific project scheme is presented in Figure 3.

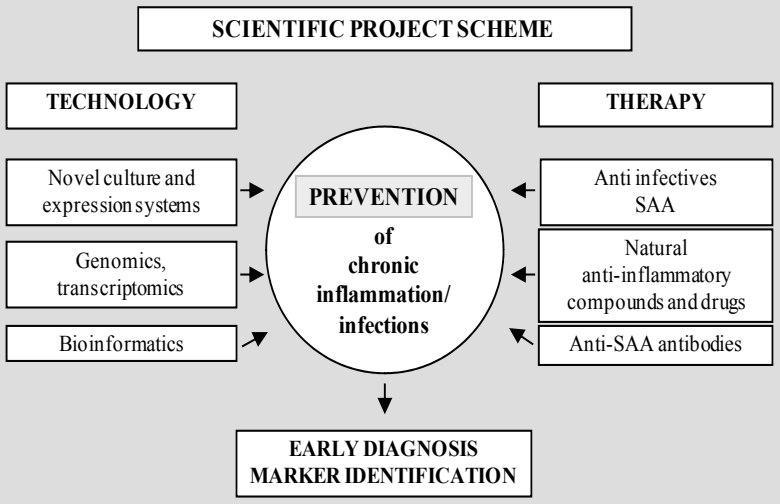

Figure 3: CODI-STRAT
A multi-disciplinary approach for earlier detection and future prevention of chronic diseases

In order to achieve the network's main aim of developing novel anti-inflammatory and anti-infective strategies, the following specific research objectives are proposed:

1. Identification of novel inflammatory markers and **SAA genetic variants** and their contribution to clinical phenotypic characteristics of asthma. Determination of the likely effects of SAA genetic variability on anti-inflammatory, antiviral, antibacterial and immunotherapeutic efficacy will be evaluated. SAA genetic variation studies will provide information with benefits, as part of a pharmacogenetic profiling system, for potential future anti-asthma therapies based on SAA inhibition.

2. Detection of very early stages of inflammation. SAA has been previously shown to correlate best with markers of RA activity, as compared to CRP or erythrocyte sedimentation rate. Very high levels of SAA were found exclusively in RA, as compared to other forms of arthritis (Cunnane et al., 2000). However, since then, there has been a lack of reports on SAA and the very early stages of RA, coupled with clinical features, including ultrasound measurements in larger longitudinal studies. So, the role of SAA and other accompanying markers will be investigated for detection of very early RA in a 3 year longitudinal study, alongside with development of prediction and forecast models of disease activity and outcome. SAA levels will also be compared between inflammatory RA and other autoimmune and non-autoimmune patient control groups.

3. Development of disease models in animals. In order to determine whether renal disease is associated with chronic inflammation and the role of SAA in parallel with other inflammatory parameters, dogs naturally infected by *Leishmania infantum* will be used. These dogs will be monitored during a period of around 12 months. In addition to inflammatory markers and

acute phase proteins (e.g. IL-6, IL-10, IL-1β, IL2-R, IL-8, TNFα, IFNγ, CRP, haptoglobin, transferrin and ferritin), serum biochemistry profile, and standard indices of renal function (microalbuminuria, creatine, protein/creatinin ratio) will be measured at the beginning of the study and 1, 2, 3, 6 and 12 months after and values obtained will be correlated with those of SAA and other inflammatory mediators. Additionally, renal biopsies will be carried out in animals in order to characterize the renal lesions according to the classifications previously reported (Costa F.A. *et al.,* 2000; Costa F.A. *et al.,* 2003).

The amelioration of inflammation by administration of anti-inflammatory drugs, such as leflunomide, methotrexate and NSAIDS will be determined. A comparison will be made between acute and chronic inflammatory models, as well as immuno-mediated inflammation and neoplasia models.

4. Determination of how SAA functions as a potential therapeutic agent in viral infections using recently developed assays and culture systems (Wakita T. *et al.,* 2005; Bartosch B. *et al.,* 2003). Briefly, a series of peptides derived from SAA will be designed based on their predicted secondary structures (Uhlar C.M. *et al.,* 1999) and their potential antiviral activity. For their antiviral functions, they will be analyzed in cell culture with the hepatitis C virus (HCVcc) using *in vitro* culture/infectivity assay system. The most potent peptides will then be used to characterize their mechanism of action. These assays will allow us to study directly the efficiency of antivirals, predict and follow the emergence of resistant mutants and investigate many other therapeutic relevant issues, such as antiviral synergy.

5. Determination of how SAA functions as a potential therapeutic agent in bacterial infections will be based on previously developed assays (Hari-Dass R. *et al.,* 2005; Shah C. *et al.,* 2006). SAA isoforms will be separated and examined for their ability to bind to selected bacteria and opsonize them (SAA-coated fluorescent beads and SAA opsonised ligand-coated fluorescent beads will be used). Studies will be performed to determine the regions of SAA responsible for binding to bacteria and responsible for binding to macrophages thus leading to phagocytosis. Initially, we will determine which naturally occurring human isoforms are responsible for binding to particularly important pathogenic Gram-negative bacteria (*e.g. E. coli, Campylobacter jejuni, Klebsiella pneumonia, Vibrio cholera* and *Salmonella sp.*). Potential antibacterial agents will be used in direct bacterial survival assays and in bacterial and epithelial cell cultures to determine the mechanism of protection as observed in previous data (Eckhardt E.R. *et al.,* 2010).

6. High throughput studies: Dedicated and whole genome microarrays will be screened for novel inflammatory markers (Fon Tacer K. *et al.,* 2007; Rezen T. *et al.,* 2007), as well as potent novel anti-inflammatory compounds determined based on their inhibitory effects in human cellular models. In addition to ELISA**,** Western blotting and flow cytometry, genomics and transcriptomics will be used to determine the consequences of SAA binding to human primary cells at transcriptional and translational levels. An advantage of this approach is the likely identification of additional molecules capable of binding SAA on cellular surfaces. All these assays will be performed using different SAA isoforms and identified genetic variants. Identifying receptors/pathways by which these isoforms can change the physiological functions of human primary cells will provide important targets for therapeutic intervention. This knowledge will also guide development of appropriate interventions either by using existing anti-inflammatory drugs or by employing novel therapeutic strategies (*e.g.* isolated compounds from marine microorganisms).

7. Bioinformatics-Data integration and modeling:

The network will identify clusters of inflammation-associated biomarkers of intermediate, well-defined specificity (markers with absolute specificity are rare or non-existing) and we anticipate that future chronic inflammatory disease diagnosis, prognosis and monitoring will rely on using computer algorithms of multiple markers, among them SAA.

Integration of heterogenous high-throughput (e.g. microarrays) and low-throughput (qPCR, Western blots, FACS) datasets is of utmost importance not only in discovering novel molecular components using model systems, but also in identifiying predictive markers using clinical samples. Therefore major thrust in this work package will be directed towards the management and integration of the generated data sets through the development of dedicated database and interfacing the database with analytical tools. Additionally, the power of mathematical modeling will be exploited to prioritize the candidate genes for further functional studies (example publications: Pages F. *et al.,* 2005; Galon J. *et al.,* 2006 and Hackl H. *et al.,* 2005).

8. Neutralization and **identification of lead therapeutic antibodies** is planned in parallel to all experiments. Existing and newly isolated SAA-specific antibodies and sera will be assessed for their ability to neutralise SAA activity. We will map the epitopes recognized by isolated neutralizing and non-neutralizing antibodies and determine whether they are conserved across genotypes, if they are linear or conformational, using competition enzyme immunoassays against native and denatured proteins and immunoassays using a panel of

point-mutated envelope proteins. The ability of monoclonal antibodies demonstrating a broad neutralizing capability to prevent pro-inflammatory activation or to neutralize SAA's protective function in infections will be assessed using *in vitro* assays, both alone and in combination, to determine whether or not synergy exists.

Lastly, the network will determine the threshold concentration and milieu conditions necessary for the transition of SAA's protective anti-infective function to one of degradative chronic nature.

Partner centers in CODI-STRAT network

Each of the following partners has long-standing experiences in their specialties, and can develop unique approaches appropriate for the identification of novel inflammatory and infective therapy strategies. By taking advantage of the great synergy that exists across the network, this integrated approach is unique and will ensure training and scientific success.
The network spans 7 European countries (5 from the Mediterranean, namely Spain, France, Italy, Malta and Slovenia) (Figure 4) and the USA.

Figure 4: Distribution of network partners across Europe.

- Austria (TUG)
- France (CNRS)
- Italy (SMVL)
- Malta (UoM)
- Slovenia (UMC-Lj, UL; IEDC, IR)
- Spain (UM, Biomar; BIOIBERICA)
- United Kingdom (LSHTM, QMUL)

Some of the countries are emerging economies, such as Slovenia and Malta, which have witnessed a steady increase of student numbers from neighbouring countries and the growing demand for training in disciplines such as bioinformatics, genomics, transcriptomics,

biopharmaceuticals, state of the art culture and expression systems and biotechnology. The network is multi-disciplinary and multi-sectorial (with industry partners/small and medium-sized enterprises, from the biopharmaceutical and nutritional fields), with excellence in science, research and training as high priorities, keeping closely connected to the clinical and biotechnical/pharmaceutical environments. Clearly important is the role of the newly formed smaller institutions, such as the Institute for Rheumatology composed of practicing physicians, diagnostic experts, research specialists and professors with the interdisciplinary knowledge and flexibility necessary for the advancement of science development, transparency and support.

There is evidence of growing successful collaboration between the partners of the CODI-STRAT network in terms of common publications (Lakota K. *et al.,* 2011; Erman A. *et al.,* 2011), as well as the 3-day attendance of the network at the SAA workshop (2010) held in IEDC-Bled School of Management (Slovenia). Prior and current collaborations have already led to exchanges of reagents and know-how. The specific partner roles in CODI-STRAT are briefly explained below.

Full Partners:

P1: The University of Primorska, Faculty of Mathematics, Natural Sciences and Information Technology (**UP-FAMNIT**), Slovenia

UP-FAMNIT represents a University/Faculty with a priority for integrated science knowledge in research and teaching, student and faculty academic excellence, autonomy and freedom towards achieving open, independent and international development. One of the goals of UP-FAMNIT is to become a reference University/Faculty locally, as well as in the Mediterranean and southeast Europe. Roles in CODI-STRAT: mathematical modelling, bioinformatics and education.

P2: The University Medical Centre-Ljubljana (**UMC-LJ**), Slovenia

The UMC-LJ is the largest public medical institution (over 7000 staff, composed of clinicians, nurses, researchers and support staff) in Slovenia promoting clinical excellence/ research/education for the benefit of patients. The Department of Rheumatology (with ~50 employees) provides the diagnostics, prognostics with the support of a fully functional routine and research laboratory (also measuring SAA routinely). Roles in CODI-STRAT: network coordination, clinical research and molecular/cellular studies.

P3: Centre national de la recherche scientifique (**CNRS**), Institut Pasteur de Lille, France

The CNRS is a public basic-research agency producing knowledge, and making it available to society. More than 1,000 research units spread throughout France cover all fields of research. The Hepatitis C Laboratory (HCL) is located on campus - Pasteur Institute of Lille is a first-rate institute renowned worldwide for its high standard in medical research, especially in the field of infectious diseases. HCL is a classical laboratory of virology containing P2 and P3 facilities with access to common facilities used for projects. HCL has trained 8 MS students and 10 PhD students, as well as 12 Post-Docs. Roles in CODI-STRAT: infectious diseases, viral models, hepatitis studies and anti-viral agents.

P4: University of Malta Medical School (**UoM**), Department of Pathology, Faculty of Medicine and Surgery, Malta

UoM is one of the oldest medical schools in Europe (founded 1676) which became University Faculty in 1771. The Department of Pathology is responsible for undergraduate teaching in all pathology disciplines, research as well as servicing medical, dental, pharmacy, health science courses. Offers postgraduate training, including MSc Biomedical Sciences (10 in 2007), collaborates closely with the Department Pharmacology & Therapeutics. Roles in CODI-STRAT: clinical studies, genetics and asthma research.

P5: University of Murcia (**UM**), Department of Veterinary Medicine and Surgery (DVM), Spain

The University of Murcia has ~ 40.000 students and 6000 staff and has recently being recognized as an University of Excellence by the Spanish Ministry of Education. The Department of Animal Medicine and Surgery (with over 60 employees) specializes in the veterinary sciences, provides teaching services and is a referral diagnostic service to small and large animal medicine. UM-DVM also specializes in the application of acute phase proteins as markers of disease, as well as indicators of disease progression, with development of sensitive immunoturbidimetric assays, production of antibodies and characterization of SAA expression in healthy and pathological samples. Roles in CODI-STRAT: veterinary studies and animal models of infectious diseases.

P6: Graz University of Technology (**TUG**), Institute for Genomics and Bioinformatics (IGB), Austria

The Institute is committed to generation, management, and leveraging of high-throughput data from genomic studies. Activities include bioinformatic education/services, development of

databases and tools for genomic data computational analysis. Methodology and equipment include: New algorithms prototyped in Matlab, R, Bioconductor or BioPerl based on established computational methods. After successful validation, algorithms - implemented. Current computational infrastructure at IGB consists of Storage Area network, with 11 TB, NAS system (1TB), 24 node dual 32-bit CPU computing cluster, seven 64-bit Opteron servers covering databases/ application services/computational analysis tasks. Staff and training experience include: IGB personnel includes 6 bioinformaticians at post-doc level and 8 at Ph.D. student level. In the past five years, 15 early stage researchers received successful PhD training. Roles in CODI-STRAT: Bioinformatics and computational analyses.

P7: Queen Mary University of London, William Harvey Research Institute (**WHRI**), UK

WHRI, Queen Mary, University of London, is the largest pharmacological Institute in the UK, rated top 20 pharmacological research centres worldwide. WHRI is a state of the art environment (~ 340 researchers) for inflammation and cardiovascular research. The Centre for Biochemical Pharmacology at the WHRI, is formed by 25 scientists and students; is equipped with 4 cell culture units, radioactive room, intravital microscopy facility, a flow chamber system etc. Close by, are state-of-the-art animal facilities, flow cytometry, Genome center and Proteomic Unit. Roles in CODI-STRAT: pharmacology, inflammation, biochemistry and molecular/cellular models.

P8: London School of Hygiene and Tropical Medicine (**LSHTM**), Department of Infectious and Tropical Diseases, UK

The London School of Hygiene & Tropical Medicine is internationally renowned in public health and tropical medicine, a leading postgraduate medical institution in Europe and Britain's national school of public health. The Department of Infectious & Tropical Diseases (~ 300 staff) is highly multidisciplinary with many MSc courses, including the well-established MSc in Immunology of Infectious Disease. Immunology unit (~ 70 staff) has a research focus on understanding infectious diseases. Roles in CODI-STRAT: infectious diseases and anti-bacterial agents.

P9: Instituto **BioMar** S.A.

Instituto Biomar, (founded in 1996) as a spin-out of the biopharmaceutical company PharmaMar, has its own building facilities in the Parque Tecnológico de León (Leon's Technological park). Last capital expansion was in 2006 and welcomed new investors. Instituto Biomar is a R&D service company working in discovery/development of natural

marine compounds for the treatment of different Human Health applications. The company has expertise in Marine Microbiology and Natural Products Chemistry, has generated large collection of natural extracts (over 35,000) from the fermentation of the marine microorganisms and a library of natural compounds (2000 entries). Its microbial strain collection is also being evaluated for other industrial applications. Roles in CODI-STRAT: biophamaceuticals, anti-inflammatory and anti-infective natural extracts.

Associate partners:

API. IEDC– Bled School of Management

IEDC – Bled School of Management was founded in 1986 as the first proper business school in Central and Eastern Europe. Over the years, it has offered more than 900 management and executive education programs to more than 50,000 managers from over 70 countries. The range of programs covers short executive development seminars and workshops and longer executive education programs, tailor-made programs for corporate partners, three MBA degree programs and a PhD program. The school accepts about 3500 program participants a year, 80% of whom come from countries other than Slovenia. Although the majority of the participants come from the corporate world, IEDC has offered a number of programs for managers of healthcare institutions and from cultural organizations, as well as public administration. Roles in CODI-STRAT: management and executive education.

APII. BIOIBERICA S.A., Spain

Bioiberica specializes in nutrition, osteoarthritis pharmacology, joint care and chondro-protection and is dedicated to biomolecular research. Roles in CODI-STRAT: pharmacology and consulting.

APIII. University of Ljubljana (**UL**)

A. Faculty of Medicine, **Institute of Cell Biology - ICB**

ICB is a facility/training site for microscopy of biological material. The facilities include transmission and scanning electron microscopy, light microscopy including life cell imaging, optical sectioning and microinjection device. ICB personnel include 9 PhD/Univ. biologists and 4 technicians. Role in CODI-STRAT: imaging specialists.

B. Faculty of Medicine, Centre for Functional Genomic and Bio-Chips (**CFGBC**), Slovenia

CFGBC is joint venture of UL & Consortium-Bio-Chips with Slovenian microarray facility/training site. The facilities include state of the art spotting arrays, oligo- and cDNA microarrays, an automatic hybridization station, scanners, high throughput RT-PCR, computers and software for data capturing data/interpretation. CFGBC personnel includes 10 PhD/Univ. biochemists/molecular biologists, 1 PhD bioinformatician, and a technician. In past ten years, 10 young investigators have received successful PhD training. Roles in CODI-STRAT: genomics, transcriptomics and biochips.

APIV. The Institute of Rheumatology **(IR)**

IR was established recently with the primary objectives of providing excellence in healthcare, diagnostics, research and education of chronic rheumatic diseases for the advancement of preventive, predictive, personalized and participatory medicine. Role in CODI-STRAT: management and clinical research consulting.

APV. University of Utah, USA (**UU**)

The University of Utah is recognized as a world leader in research, having the overall goals of advancing the frontiers of knowledge, enriching society, and serving the greater good. To meet these goals, the University actively promotes the recruitment of world-class scientists through various programmes and substantial investment into core facilities, state-of-the-art equipment, and support personnel needed to carry out cutting edge research. The UU's research and scholarly activity is ranked 80th in the world and 47th in the United States in the 2009 Academic Ranking of World Universities (www.arwu.org/ARWU2009.jsp). Also in 2009, the UU was ranked among the top 25 public U.S. research universities and among the top 50 U.S. research universities overall (Top American Research Universities report; www.mup.asu.edu/research.html). Specific emphasis on advancing human health issues is evident from our internationally recognized research in the areas of microbial pathogenesis, immunology and cell biology within the Division of Microbiology and Immunology (~26 faculty) in the Pathology Department. Roles in CODI-STRAT: infectious diseases, microbiology and animal models.

APVI. San Marco Veterinary Laboratory (**SMVL**)

SMVL is the largest veterinary laboratory in Italy, specializing in animal care and acute phase proteins. SMVL has a strong interest in clinical research and dissemination of scientific

knowledge to veterinary doctors. Roles in CODI-STRAT: veterinary studies, animal models and animal care.

CONCLUSIONS

There is urgency for the development of novel, effective and safer anti-inflammatory drugs and anti-infectious agents, making this network more than timely. This coordinated cohort effort can provide novel strategies for rapid development of anti-inflammatory drugs and anti-infectious agents to the Mediterranean region, as well as broader European and international communities. This network will work to develop the necessary multi-disciplinary and multi-sectorial approach to bring about the rapid development of detection kits and therapeutics leading from bench to the bedside, resulting in improved health and welfare together with significant direct and indirect economic, as well as social benefits.

AKNOWLEDGEMENTS

The CODI-STRAT consortium would like to warmly thank IEDC-Bled School of Management and IR-The Institute of Rheumatology, Slovenia for their support.

REFERENCES

Bartosch, B., J. Dubuisson and F.L. Cosset. 2003. Infectious hepatitis C virus pseudo-particles containing functional E1-E2 envelope protein complexes. *J Exp Med* 197(5): 633-42.

Costa, F.A., J.L. Guerra, S.M. Silva et al. 2000. CD4(+) T cells participate in the nephropathy of canine visceral leishmaniasis. *Braz J Med Biol Res* 33(12): 1455-8.

Costa, F.A., H. Goto, L.C. Saldanha et al. 2003. Histopathologic patterns of nephropathy in naturally acquired canine visceral leishmaniasis. *Vet Pathol* 40(6): 677-84.

Cunnane, G., S. Grehan, S. Geoghegan et al. 2000. Serum amyloid A in the assessment of early inflammatory arthritis. *J Rheumatol* 1: 58-63.

de Jesus Rodriguez, B., C. Chevaleyre, G. Henry et al. 2009. Identification in milk of a serum amyloid A peptide chemoattractant for B lymphoblasts. *BMC Immunol* 10:4.

Eckersall, P.D. and R. Bell. 2010. Acute phase proteins: Biomarkers of infection and inflammation in veterinary medicine. *Vet J* 185(1): 23-7.

Eckhardt, E.R., J. Witta, J. Zhong et al. 2010. Intestinal epithelial serum amyloid A modulates bacterial growth in vitro and pro-inflammatory responses in mouse experimental colitis. *BMC Gastroenterol* 10:133.

Erman, A., K. Lakota, K. Mrak-Poljsak et al. 2011. Uropathogenic *Escherichia coli* Induces Serum Amyloid A in mice following urinary tract and systemic inoculation. *PloS One in submission*.

Fon Tacer, K., D. Kuzman, M. Seliskar et al. 2007. TNF-alpha interferes with lipid homeostasis and activates acute and proatherogenic processes. *Physiol Genomics* 31(2): 216-27.

Galli, S.J., M. Tsai and A.M. Oiliponsky. 2008. The development of allergic inflammation. *Nature* 454: 445-54.

Galon, J., A. Costes, F. Sanchez-Cabo et al. 2006. Type, density, and location of immune cells within human colorectal tumors predicts clinical outcome. *Science* 313: 1960-4.

Hackl, H., T.R. Burkard, A. Sturn et al. 2005. Molecular processes during fat cell development revealed by gene expression profiling and functional annotation. *Genome Biol*. 6: R108.

Hari-Dass, R., C. Shah, D.J. Meyer et al. 2005. Serum Amyloid A Protein Binds to Outer Membrane Protein A of Gram-negative Bacteria. *J Biol Chem* 280: 18562-7.

Johnson, B.D., K.E. Kip, O.C. Marroquin et al. 2004. Serum amyloid A as a predictor of coronary artery disease and cardiovascular outcome in women: the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 109(6): 726-32.

Katayama, T., H. Nakashima, C. Takagi et al. 2005. Prognostic value of serum amyloid A protein in patients with acute myocardial infarction. *Circ J* 69(10): 1186-91.

Lakota, K., G.G. Thallinger, S. Cucnik et al. 2011. Could antibodies against Serum Amyloid A function as physiological regulators in humans? *Autoimmunity* 44(2): 149-58.

Lakota, K., K. Mrak-Poljsak, B. Rozman et al. 2010. Serum Amyloid A and Its Potential Physiological / Pathological Functions - An Overview of Patents. *Recent Patents on Endocrine Metabolic & Immune Drug Discovery* 4: 89-99.

Lavie, M., C. Voisset, N. Vu-Dac et al. 2006. Serum amyloid A has antiviral activity against hepatitis C virus by inhibiting virus entry in a cell culture system. *Hepatology* 44: 1626-34.

Malle, E. and F.C. De Beer. 1996. Human serum amyloid A (SAA) protein: a prominent acute-phase reactant for clinical practice. *Eur J Clin Invest* 26: 427-35.

Malle, E., S. Sodin-Semrl and A. Kovacevic. 2009. Serum amyloid A: an acute-phase protein involved in tumour pathogenesis. *Cell Mol Life Sci* 66(1): 9-26.

Medzhitov, R. 2008. Origin and physiological roles of inflammation. *Nature* 454: 428-35.

Miwata, H., T. Yamada, M. Okada et al. 1993. Serum amyloid A protein in acute viral infections. *Arch Dis Child* 68(2): 210-4.

Molenaar, A.J., D.P. Harris, G.H. Rajan et al. 2009. The acute-phase protein serum amyloid A3 is expressed in the bovine mammary gland and plays a role in host defence. *Biomarkers* 14(1): 26-37.

Morrow, D.A., N. Rifai, E.M. Antman et al. 2000. Serum amyloid A predicts early mortality in acute coronary syndromes: A TIMI 11A substudy. *J Am Coll Cardiol* 35(2): 358-62.

Pages, F., A. Berger, M. Camus et al. 2005. Effector memory T cells, early metastasis, and survival in colorectal cancer. *N Engl J Med* 353: 2654-66.

Rezen, T., J.A. Contreras and D. Rozman 2007. Functional genomics approaches to studies of the cytochrome p450 superfamily. *Drug Metab Rev* 39(2-3): 389-99.

Shah, C., R. Hari-Dass and J.G. Raynes. 2006. Serum amyloid A is an innate immune opsonin for Gram negative bacteria. *Blood* 108: 1751-7.

Sjöwall, C. and J. Wetterö. 2007. Pathogenic implications for autoantibodies against C-reactive protein and other acute phase proteins. *Clin Chim Acta* 378(1-2): 13-23.

Sodin-Semrl, S., A. Spagnolo, R. Mikus et al. 2004. Opposing regulation of interleukin-8 and NF-kappaB responses by lipoxin A4 and serum amyloid A via the common lipoxin A receptor. *Int J Immunopathol Pharmacol* 17(2): 145-56.

Uhlar, C.M. and A.S. Whitehead. 1999. Serum amyloid A, the major vertebrate acute-phase reactant. *Eur J Biochem* 265: 501-23.

Wakita, T., T. Pietschmann, T. Kato et al. 2005. Production of infectious hepatitis C virus in tissue culture from a cloned viral genome. *Nat Med* 11: 791-6.

Weiss, U. 2008. Inflammation. *Nature* 454(7203): 427.

Wetterö, J, L. Nilsson, L. Jonasson et al. 2009. Reduced serum levels of autoantibodies against monomeric C-reactive protein (CRP) in patients with acute coronary syndrome. *Clin Chim Acta* 400(1-2): 128-31.