INFLA-CARE e-Newsletter

The e-newsletter of the FP7-funded integrated project 'INFLA-CARE'

Issue 3 *March 2013*

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Website and newsletter produced by the *INFLA-CARE* Management Office

Note from the Project Coordinator

Welcome to the 3rd and final edition of the INFLA-CARE e-News letter, the publication of the European Commission-funded research project INFLA-CARE. As the funding period for INFLA-CARE draws to a close, we feature more of our consortium members in this issue and list our publications for the period 2012-2013. Our editorial this time looks at the challenges facing research and development (R&D) and we have a review of our 4th Annual Meeting and Summer School which were held in September 2012. I do hope you enjoy this issue and that INFLA-CARE news will reach a wide audience who share an interest in our science.

INFLA-CARE research cited

Recently, INFLA-CARE project officer Jan Van De Loo at the European Commission, Health Directorate, had a paper published in the journal *The Oncologist*, entitled *"Emphasising the European Union's Commitment to Cancer Research: A Helicopter View of the Seventh Framework Programme for Research and Technological Development"*. In this paper Van De Loo and colleagues outline the benefits and impact of collaborative research funded by FP7. They cite INFLA-CARE as an example of how European funding for cancer research is addressing the issue of the outcome of cancer and state that "the INFLA-CARE project (€12 million), which focuses on the role of inflammation in cancer, has developed novel mouse models of hepatocellular carcinoma and colitis associated cancer, as well as novel therapeutic approaches including synthetic compounds, immunotherapy, and immune status-tailored chemotherapeutic strategies for gastrointestinal stromal tumours, which are likely to influence clinical practise."

The reference to INFLA-CARE as an example of successful European funding is an important accreditation to our work as a consortium over the last 4 years.

[Oncologist. 2012;17(10):e26-32. doi: 10.1634/ theoncologist.2012-0327]

Meet our team – 4 more members of INFLA-CARE come under the spotlight

Ron Apte joined the Ben Gurion University Faculty of Sciences in 1981. The major focus of research in his lab is inflammation in malignant processes. The pioneering studies

of Apte's group demonstrated the feasibility of intervening in the malignant process by neutralizing inflammatory components in the "normal" microenvironment of a tumor. They also detailed the basic concepts underlying such treatment. Interleukin-1 (IL-1), in particular has been studied for years by Ron's group. They have treated tumor-bearing mice with a specific inhibitor of IL-1, known as the IL-1 receptor antagonist (IL-Ra), and succeeded in weakening the tumor's invasiveness. IL-Ra, in its generic form Anakirna, is a medication that efficiently alleviates symptoms of patients suffering from rheumatoid arthritis, a chronic inflammatory disease.

Ron holds the Irving Sklar Chair in Endocrinology and Cancer and was awarded the 2010 Samuel and Paula Elkeles Prize for Outstanding Scientist in the Field of Medicine.

Sinisa Volarevic has been Professor of Molecular Medicine at the University of Rijeka, Croatia since 2001. The main interest of his group is the study of ribosomal protein (RP) deficiencies in mammals. They demonstrated that inducible deletion of the RPS6 gene in the liver of adult mice inhibits the synthesis of the 40S ribosomal subunit as well as proliferation of liver cells following partial hepatectomy, despite seemingly unaffected protein synthesis. These observations suggested the existence of a novel checkpoint, downstream of the deficiency in ribosome biogenesis. More recently, *in vivo* studies provided convincing evidence for the existence of this checkpoint and demonstrated that the p53 tumor suppressor is its critical component. Sinisa's group continues to work on understanding the molecular basis of this checkpoint response and determining its role in pathogenesis of various diseases.

Following several years spent at the Institute for Cancer Studies in Birmingham, UK and a spell at the Kimmel Cancer Research Centre, Philadelphia, USA, **Aris Eliopoulos** moved to the University of Crete in 2005. He now heads a team of 10 researchers and support staff, based at the University of Crete Medical School and the IMBB research institute nearby. The Eliopoulos lab is involved in unraveling signaling pathways in inflammation and cancer. His research has also contributed to the field of CD40 receptor signaling and function and has led to discoveries relevant to clinical practice.

Laurence Zitvogel is the Research Director at Institut National de la Santé et Recherche Médicale in a laboratory located at Institut GrustaveRoussy, Villejuif, France. She graduated in 1992 with a degree in Medical Oncology from the School of Medicine of the University of Paris, France. She began her scientific career at the University of Pittsburgh, USA working under Michael Lotze. Her expertise is dendritic cell and innate effector biology and relevance during tumor development, as well as exosome-based vaccine designs.

INFLA-CARE's Scientific Advisory Board

As the INFLA-CARE programme draws to a close, we look at the important work of our Scientific Advisory Board. These distinguished scientists are unpaid for their time spent on our consortium and yet they provide an essential and valued guiding hand for programmes such as INFLA-CARE. Members of the SAB attend the consortium annual meetings where possible, to follow the progress and monitor activities of the programme. They also have the responsibility of writing an independent report which is submitted to the EC for review and is distributed among the consortium to provide feedback and direction for the future running time of the project.

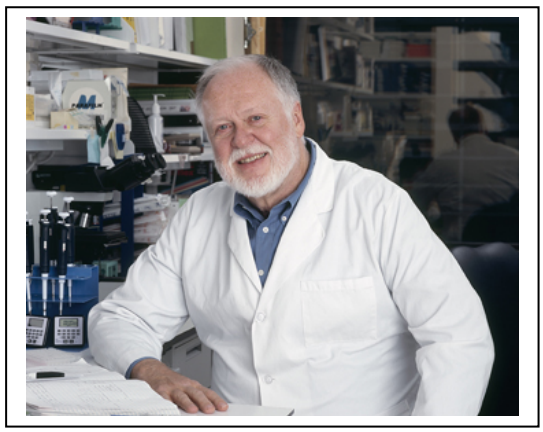
INFLA-CARE has been fortunate to have a SAB featuring 3 distinguished and committed scientists. We feature a brief description of their scientific interests below and thank them sincerely for their valued time and the enthusiasm they have brought to the programme.

Vishva Dixit joined Genentech in 1997 to be Director of Molecular Oncology because, he says, the position offered a great opportunity to turn the bench-side science he had been doing into therapeutics that could make a meaningful impact on the lives of cancer patients. Staff at Vishva's laboratory study the apoptotic and NF-κB signaling pathways. More recently they have also become interested in the role of ubiquitin hydrolases as regulators of these and related pathways. Vishva's team is also investigating regulatory components of the innate immune system, including adaptors that activate pro-inflammatory caspases in response to intracellular pathogens or engagement of Toll like Receptors. Vishva Dixit has received numerous awards in recognition of his major contributions to biomedical research.

Poul Sorensen studied medicine at UBC and McGill University and following a spell as a pathologist, he was awarded a research chair at the University of British Columbia. His lab

studies signal transduction pathways in childhood malignancies and in particular how gene rearrangements or mutations disrupt signal transduction in pediatric tumors, or how genome-wide changes in gene expression relate to signaling alterations in these tumors. He has received a number of honours and awards.

Curtis C. Harris received his M.D. from Kansas University School of Medicine and he completed his clinical training in internal medicine at the University of California-Los Angeles, and at the NCI. He has held



positions of increasing responsibility at the NCI, and is the Head of the Laboratory of

Human Carcinogenesis and chief of its Molecular Genetics and Carcinogenesis Section. He is also a Clinical Professor of Medicine and Oncology at Georgetown University School of Medicine. The outstanding scientific contributions of Curt to the fields of molecular carcinogenesis and molecular epidemiology of human cancer, have placed him at the forefront of international science. His research on environmental carcinogenesis, cancer risk factors and molecular genetics of human carcinogenesis, p53 and microRNA pathways, has had a significant impact on the field of cancer risk assessment and our understanding of the molecular pathogenesis of human cancer. He holds numerous awards and is Editor-in-Chief of *Carcinogenesis*.

Editorial: Research and Development – what's new on the Horizon

'Research and development' (R&D) is usually understood as the discovery of new scientific knowledge to enable the development of valuable products, processes or services. In this short editorial we look at why R&D is essential to science and society, some constraints that currently act on it and how Europe is placing the principles of R&D at the centre of its new scientific funding programme Horizon 2020.

Scientific research has an important multi-faceted role in our society; through research we achieve knowledge which is important for its own sake, but research is also fertile ground for innovation and development of ideas which are important for our world tomorrow. While industry takes and develops ideas from research to provide society with new technology, the main 'customers' of research today are governments who use research they have funded to help them make informed decisions and to assist in policy making.

Something which fascinates and frustrates many scientists is the issue of how much external control is needed for R&D to be successful, as most discoveries simply aren't planned in advance. To attract funding to do basic research however, scientists must usually justify a detailed plan in advance of their work and must periodically report to the funding body on the progress of the research. However it is widely recognized that although risky and without guarantees, complete freedom for scientists to manage the direction of research boosts creativity and productivity. So although goal-oriented science is safer to fund, it may never create the same opportunities for creativity and innovation.

Problems in R&D are not just restricted to the creativity but are also present further down the line where potentially interesting ideas never make it through to development. For companies, R&D is an uncertain investment and not an activity undertaken for immediate profit. This explains the so-called 'valley of death' that exists between basic research and commercialization; many potentially valuable results are never taken further, on account of the risk that they will not prove useful.

These two issues which hamper R&D can be partly resolved by skillfully directed funding, trust-based review and investment in a knowledge based economy. Funding bodies who ask the 'right' questions to direct their funds appropriately and allow researchers the intellectual space and trust to proceed instinctively with their research, will reap the benefits of inspired and innovative research.

The bringing together of academic and industrial partners in EC-funded programmes has begun to address the shortfall of ideas that never make it off the bench. The 7th framework programme of the EC funded the formation of academia/industry alliances and was successful in bringing its members together in a committed and focused manner.

As the period of FP7 funding draws to a close, the EC has launched its successor, **Horizon**

2020; an 80 billion euro EU framework programme for research and technical development. The aim of Horizon 2020 is to fund innovation and technology to address the challenges to society, health, energy and transport, in a forum which brings together the main players in R&D: companies, universities and institutes. Horizon 2020 aims to encourage the flow of knowledge between these separate entities to create an environment where innovation can flourish and the benefits are translated into new growth and jobs in Europe which can benefit every European citizen.

4th Annual Meeting and Summer School

INFLA-CARE's 4th and final annual meeting took place in September 2012, in Malia, Crete, Greece. The meeting was well attended and we were fortunate to be able to welcome all three members of our Scientific Advisory Board: Curt Harris, Poul Sorensen and Vishva Dixit. It was immensely rewarding to see so many projects coming close to fruition and to observe how INFLA-CARE young researchers have grown in confidence and capability over the 4 years that the programme has funded their work. The consortium were praised unanimously by the SAB for their commitment and quality of research in INFLA-CARE. Many scientists and others connected to the programme have commented on how INFLA-CARE has been a singular programme of the highest scientific quality and how, regrettably, our current strong and productive official collaboration will soon come to an end. Fortunately however, we were able to secure a 6-month extension to INFLA-CARE from the EC to cover some unavoidable delays to projects which occurred at the beginning of the programme.

The INFLA-CARE summer school (*2nd Inflammation, Cancer and Novel therapeutics Conference and Summer School*) was this year run in collaboration with two other EC-funded programmes, *TACIT* (Targeted Oligo-nucleotide Carriers in Immunotherapy) and *TransPOT* (Translational Research Potential in Human Diseases). This joint summer school programme was planned to increase the dissemination of knowledge of the event and bring our research to as wide an audience as possible.

Professor Philip Tsichlis, Tufts, USA, speaker at the Summer School.

In addition to speakers selected from the INFLA-CARE, TACIT and TransPOT programmes, we were delighted to welcome Philip Tschilis (USA), Karin de Visser (Netherlands), Vishva Dixit (USA), Poul Sorensen (Canada), Christoph Becker (Germany), George Apidianakis (Cyprus), Curt Harris (USA), Dimitris Boumpas (Greece) and Vily Panoutsakopoulou (Greece) to give invited talks. In response to feedback from our last summer school run in 2012, this time the event was run over 4 days, with poster sessions slotted into the schedule to give a less hectic programme.

The location of both these INFLA-CARE events at the Ikaros Village Resort and Spa with beautiful coastal surroundings and excellent services provided by the hotel was commented by the delegates.

Recently Awarded Programmes

Two members of the INFLA-CARE consortium have recently attracted further EC FP7 funding through the Regional Potential call, which helps converging regions of Europe reach their full potential, by bringing infrastructure and talented personnel to the area. **Aris Eliopoulos** coordinated a University of Crete Medical School team which has been awarded *TransPOT*, a 3 million euro grant which aims to boost translational research efforts at the University of Crete Medical School. The programme will equip and run state-of-the-art Genomics and GMP Cell Therapy facilities. **Vassilis Gorgoulis** from the University of Athens is also participating in a regional potential consortium called INsPiRE – integrating the emerging research potential of the University of Athens Cancer Research Group in the translational research area.

Publications

A selection of INFLA-CARE related publications for 2012/13:

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Mutant p53 prolongs NF-κB activation and promotes chronic inflammation and inflammation-associated colorectal cancer. Cooks T, Pateras IS, Tarcic O, Solomon H, Schetter AJ, Wilder S, Lozano G, Pikarsky E, Forshew,T, Rozenfeld N, Harpaz N, Itzkowitz S, Harris CC, Rotter V, Gorgoulis VG, and Oren M. ***Cancer Cell***, 2013 in press.

The transcription of the alarmin cytokine interleukin-1 alpha is controlled by hypoxia inducible factors 1 and 2 alpha in hypoxic cells. Rider P, Kaplanov I, Romzova M, Bernardis L, Braiman A, Voronov E, Apte RN. ***Front Immunol.*** 2012;3:290

Monocytes-macrophages that express α-smooth muscle actin preserve primitive hematopoietic cells in the bone marrow. Ludin A, Itkin T, Gur-Cohen S, Mildner A, Shezen E, Golan K, Kollet O, Kalinkovich A, Porat Z, D'Uva G, Schajnovitz A, Voronov E, Brenner DA, Apte RN, Jung S, Lapidot T. ***Nat Immunol.*** 2012 Nov;13(11):1072-82.

Identification of a genetic locus controlling bacteria-driven colitis and associated cancer through effects on innate inflammation. Boulard O, Kirchberger S, Royston DJ, Maloy KJ, Powrie FM. ***J Exp Med***. 2012 Jul 2;209(7):1309-24

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The Drosophila DUSP puckered is phosphorylated by JNK and p38 in response to arsenite-induced oxidative stress. Karkali K, Panayotou G. ***Biochem Biophys Res Commun.*** 2012 Feb 10;418(2):301-6

Tumor progression locus 2/Cot is required for activation of extracellular regulated kinase in liver injury and toll-like receptor-induced TIMP-1 gene transcription in hepatic stellate cells in mice. Perugorria MJ, Murphy LB, Fullard N, Chakraborty JB, Vyrla D, Wilson CL, Oakley F, Mann J, Mann DA. ***Hepatology.*** 2013 Mar;57(3):1238-49

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SnapShot: p38 MAPK Substrates. Trempolec N, Dave-Coll N, Nebreda AR. ***Cell***. 2013 Feb 14;152(4):924-924

SnapShot: p38 MAPK Signaling. Trempolec N, Dave-Coll N, Nebreda AR. ***Cell***. 2013 Jan 31;152(3):656-656

Specific lipofuscin staining as a novel biomarker to detect replicative and stress-induced senescence. A method applicable in cryo-preserved and archival tissues.Georgakopoulou EA, Tsimaratou K, Evangelou K, Fernandez-Marcos PJ, Zoumpourlis V, Trougakos IP, Kletsas D, Bartek J, Serrano M, Gorgoulis VG. ***Aging*** (Albany NY). 2013 Jan 5;5(1):37-50

Macrophages, nitric oxide and microRNAs are associated with DNA damage response pathway and senescence in inflammatory bowel disease. Sohn JJ, Schetter AJ, Yfantis HG, Ridnour LA, Horikawa I, Khan MA, Robles AI, Hussain SP, Goto A, Bowman ED, Hofseth LJ, Bartkova J, Bartek J, Wogan GN, Wink DA, Harris CC. ***PLoS One.*** 2012;7(9)

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Histone Displacement during Nucleotide Excision Repair. Dinant C, Bartek J, Bekker-Jensen S. ***Int J Mol Sci.*** 2012 Oct 17;13(10):13322-37

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Autocrine VEGF-VEGFR2-Regulation of stem cell plasticity: mechanisms and relevance to tissue biology and cancer. Strauss R, Hamerlik P, Lieber A, Bartek J. ***J Exp Med.*** 2012 Mar 12;209(3):507-20

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Mutual protection of ribosomal proteins L5 and L11 from degradation is essential for p53 activation upon ribosomal biogenesis stress. Bursać S, Brdovčak MC, Pfannkuchen M, Oršolić I, Golomb L, Zhu Y, Katz C, Daftuar L, Grabušić K, Vukelić I, Filić V, Oren M, Prives C, Volarević S. ***Proc Natl Acad Sci USA***, 2012; 109: 20467-72

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