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THE DEATH OF PLANT CELLS

FROM PROTEASES TO FIELD APPLICATIONS

October, 2nd, 3rd and 4th, 2013

CosmoCaixa. C/ Isaac Newton, 26. Barcelona

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BARCELONA

"B·Debate strives to help position Barcelona as a benchmark in generating knowledge and Catalonia as a country of scientific excellence"

B·Debate is an initiative of Biocat with support from "la Caixa" Foundation which aims to drive top-notch international scientific events to foster debate, collaboration and open exchange of knowledge among experts of renowned national and international prestige. The debates are focused on the integration of diverse disciplines of science in order to tackle major scientific and societal challenges.

DEATH OF PLANT CELLS

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THE DEATH OF PLANT CELLS

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WELCOME

Dear Invited Speakers and Participants,

We are pleased to welcome you to Barcelona and to the meeting "**The death of plant cells: from proteases to field applications**", co-organised by B·Debate International Center for Scientific Debate Barcelona, an initiative of Biocat with the support of "la Caixa" Foundation and the Center for Research in Agricultural Genomics (CRAG).

Plant research at the molecular level is coming of age and plant programmed cell death (PCD) is now known to play central roles in both plant health and disease. The debate comes at a time of heightened need for novel (elegant) second-generation crops that not only grow better in healthy conditions, but are also able to fight recalcitrant diseases. We have focused this debate on the role of proteases in PCD, as they are key orchestrators of this process, and on studying the differences and commonalities of the PCD mechanisms in various organisms. A constructive dialogue of expert researchers from a multitude of fields converging around plant PCD will strengthen a common research base in Europe and the world. Complementing this base with specialists in PCD in other organisms and agbiotech companies is instrumental to identify future challenges and key bottlenecks in our understanding of the process and to be able to translate novel findings to crops or even beyond, to human health.

On behalf of CRAG and B·Debate, we thank you for joining us in this exciting debate, which we are confident that will foster the understanding of PCD and its applications in agriculture. We encourage you to participate actively in the discussions.

Sincerely yours,

Nuria Sànchez-Coll, **Marc Valls** (Scientific Leaders) and **B·Debate**

PROGRAM

Wednesday, October, 2nd, 2013

8:30 **Registration**

8:45 **Welcome**

Laia Arnal, Head of Research and Scientific Debate, Biocat
Nuria Sànchez-Coll, Researcher at the Center for Research in Agricultural Genomics (CRAG)

9:00 **SESSION 1: MODE OF ACTION OF PROTEASES AND BIOTECHNOLOGY APPLICATIONS**

Chair: **Simon Stael**, Flemish Institute for Biotechnology (VIB), Ghent, Belgium

Evolution of Secreted immune Proteases and Their inhibitors
Renier van der Horn, Max Planck Institute, Cologne, Germany

9:30 **Serpins Control Cell-death Proteases During Biotic and Abiotic Stress**
Robert Flurh, Weizmann Institute of Science, Israel

10:00 **Protease interactions Regulating ER-stress induced PCD in *Arabidopsis***
Patrick Gallois, University of Manchester, United Kingdom

10:30 **Coffee break**

11:00 **Positional Proteomics Approaches for Protease Degradomics**
Kris Gevaert, Flemish Institute for Biotechnology (VIB), Ghent University, Ghent, Belgium

11.30 **Metacaspase Degradomics**
Frank Van Breusegem, Flemish Institute for Biotechnology (VIB), Ghent University, Ghent, Belgium

12:00 **Potential Biotech Applications of Cysteine-proteases and Their Inhibitors**
Isabel Díaz, Centro de Biotecnología y Genómica de Plantas (CBGP), Madrid, Spain

12:30 **Lunch**

14:00 **SESSION 2: THE ROLE OF PROTEASES DURING DEVELOPMENTAL PCD**

Chair: **Moratz Nowack**, Flemish Institute for Biotechnology (VIB), Ghent, Belgium

Cell-autonomous and Organismal Roles of Autophagy in Plant Development
Peter Bozhkov, Uppsala BioCenter, Uppsala, Sweden

14:30 **Post Mortem Program During Developmental Cell Death in *Arabidopsis***
Hanele Tuominen, Umeå Plant Science Center, Umeå, Sweden

15:00 **Integrating the Signaling Networks That Trigger Programmed Cell Death in Self-Incompatible *Papaver* Pollen**

Veronica Franklin-Tong, University of Birmingham, Birmingham, United Kingdom

15:30 **Coffee break**

PROGRAM

Wednesday, October, 2nd, 2013

16:00 **The Troublesome Transition: Programmed Cell Death During Plant Reproduction**
Moritz Nowack, Flemish Institute for Biotechnology (VIB), Ghent, Belgium

16:30 **Impact of Deletion of the Metalloprotease FtsH11 in *Arabidopsis thaliana***
Christiane Funk, Umea University, Umea, Sweden

17:00 **Tapetal Cell Death.The Way To Pollen Fertility**
Zoe Wilson, University of Nottingham, Nottingham, United Kingdom

17:30 **The Ubiquitin Ligase Mutant saul1-an inducible Model System for Developmental Cell Death**
Stefan Hoth, University Hamburg, Hamburg, Germany

18:00 **Visit to Cosmocaixa**

19:00 **Cocktail at Cosmocaixa**

Thursday, October, 3rd, 2013

8:45 **SESSION 3: PATHOGEN-TRIGGERED PCD AND THE ROLE OF PROTEASES DURING IMMUNE RESPONSES**

Chair: **Marc Valls**, Centre for Research in Agricultural Genomics (CRAG), Barcelona, Spain

Effector Specialization Following a Host jump in the Irish Potato Famine Pathogen Lineage
Sophien Kamoun, Sainsbury Laboratory, Norwich, United Kingdom

9:15 **Modulation of Apoplastic Immunity in the *Ustilago maydis* – Maize Interaction**
Gunther Doehlemann, Max Planck Institute, Marburg, Germany

9:45 **The Role of Plant and Fungal Proteases in Fungus-plant interaction with Emphasis on the Pathosystem *Cladosporium Fulvum*-tomato**
Pierre De Wit, Wageningen University, Wageningen, The Netherlands

10:15 **Coffee break**

11:00 **Metacaspase Complexes Regulating HR Cell Death**
Nuria Sànchez-Coll, Center for Research in Agricultural Genomics (CRAG), Barcelona, Spain

11:30 **Transcriptional Control of *Arabidopsis hypersensitive* Cell Death in Response to Bacterial Pathogens**
Susana Rivas, Laboratory of Plant-Microbe Interactions, INRA, Toulouse, France

12:00 **Endomembrane Systems Responsible for Defense Strategies of Plants**
Ikuko Hara-Nishimura, Kyoto University, Kyoto, Japan

12:30 **Lunch**

PROGRAM

Thursday, October, 3rd, 2013

14:00	Chair: **Nuria Sànchez-Coll**, Center for Research in Agricultural Genomics (CRAG), Barcelona, Spain
	Pleiotropic Effects of Autophagy and NPR1 Deficiencies in Cell Death During Immune Responses and Development **Morten Petersen**, University of Copenhagen, Copenhaguen, Denmark
14:30	**Functions and Regulation of ATG8-Mediated Autophagy in Plants** **Richard Vierstra**, University of Wisconsin-Madison, Madison, USA
15:00	**Coffee break**
15:30	**Open Debate**
17:00	**Free evening**

Friday, October, 4th, 2013

8:45	**SESSION 4: WHAT CAN WE LEARN FROM PCD AND PROTEASES IN OTHER SYSTEMS?**
	Chair: **Frank Van Breusegem**, Flemish Institut for Biotechnology (VIB)Ghent University, Ghent, Belgium
	Caspases and Paracaspases in Cell Death and Survival Networks **Guy Salvesen**, Sanford-Burnham Medical Research Institute, La Jolla, USA
9:15	**Necrosis, Typical and Atypical Apoptosis Induced by Glucose Deprivation in Cancer Cells. Role of autophagy** **Cristina Muñoz-Pinedo**, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain
9:45	**Structural insights into Why Metacaspases Are Not Caspases** **Karen McLuskey**, University of Glasgow, Glasgow, United Kingdom
10:15	**Cell Death in *Dictyostelium*** **Pierre Golstein**, Centre d'Immunologie de Marseille-Luminy, Marseille, France
10:45	**Coffee break**
11:15	**Strategies to Identify Ligands, inhibitors and Naturals Substrates of Carboxypeptidases and Other Proteolytic Enzymes** **Francesc Xavier Avilés**, IBB and Universitat Autònoma de Barcelona, Barcelona, Spain
11:45	**Open Debate**
13:00	**Closing remarks**
13:15	**Lunch**

SCIENTIFFIC COMMITTE

Nuria Sànchez-Coll, Reserchер at the **Center for Research in Agricultural Genomics (CRAG)** Barcelona, Spain

Nuria Sànchez-Coll obtained her PhD degree at the Swiss Federal Institute of Technology (ETH-Zürich) in 2006 under Dr. Klaus Apel direction. Her work is focused on the signalling pathways leading to programmed cell death in response to reactive oxygen species. She then joined the lab of Dr. Jeff Dangl at the University of North Carolina with a Swiss National Research Foundation fellowship to study the role of metacaspases during pathogen-triggered hypersensitive response cell death. In 2012 she moved to the recently created Centre of Research in Agricultural Genomics (CRAG) in Barcelona with a Marie Curie Career Integration Grant and a Beatriu de Pinós fellowship. In 2013 she has obtained the Sala-Trepat award from the Catalan Society of Biology for her work in molecular biology. She is currently co-leading the "Bacterial Pathogens and Plant Cell Death" team at CRAG together with Dr. Marc Valls (www.ub/edu/bactplantdiseases). Her work focuses on the role of type I metacaspases in pathogen and developmental programmed cell death in plants.

Marc Valls, Associate Professor at **Universitat de Barcelona** and Researcher at the **Center for Research in Agricultural Genomics (CRAG)** Barcelona, Spain

Marc Valls obtained in 2000 his PhD degree in Genetics at the Universitat de Barcelona for his work on heavy metal-chelating proteins. He then moved to the study of bacterial transcription as a postdoc in the National Biotechnology Center in Madrid. He performed a second postdoc in the INRA in Toulouse where he started to work in virulence gene regulation in the bacterial plant pathogen *Ralstonia solanacearum*. He then moved back to Universitat de Barcelona, obtaining an Associate Professor position in 2008 and continuing his research on the genetics of plant-pathogen interactions. He joined the CRAG in 2010, where he currently co-leads together with Dr. Nuria Sànchez-Coll the "Bacterial Pathogens and Plant Cell Death" team. His recent research has focused on improving the genetic modification of *R. solanacearum* and deciphering the genetic program that this pathogen deploys to infect plants and cause the bacterial wilt disease.

Frank Van Breusegem, Professor at **Ghent University** and Researcher at the **Flemish Institute for Biotechnology (VIB)**, Ghent, Belgium

Frank Van Breusegem obtained a degree in Biotechnology at Ghent University in 1997 with a study on increased abiotic stress resistance in transgenic corn. Nowadays, he is a principal investigator at the Plant Systems Biology department of the Flanders Institute for Biotechnology and is a professor in Plant Biotechnology at Ghent University. In his research, he mainly focuses on signal transducing events triggered by increased levels of reactive oxygen species and on the development of new technologies to study plant growth and development to pinpoint gene networks that are potential candidates for innovative molecular breeding strategies to develop biotech crops with improved traits. Van Breusegem also played a pioneering role in the functional analysis of plant metacaspases.

Moritz Nowack, Researcher at the **Flemish Institute for Biotechnology (VIB)**, Ghent, Belgium

Moritz K. Nowack is a Junior Group Leader at the Plant Systems Biology Department (PSB) at the Flemish Institute for Biotechnology (VIB) and the University of Ghent, Belgium. He received his Ph.D. in 2007 from the University of Cologne, Germany, after having worked as an International Max-Planck Research School (IMPRS) Ph.D. fellow at the Max-Planck Institute for Plant Breeding Research (MPIPZ) and the University of Cologne. During his Ph.D. research, he investigated the role of cell cycle regulation during plant reproductive development. After a follow-up post-doc period at the MPIPZ and the Institut de Biologie Moléculaire des Plantes (IBMP) in Strasbourg, he obtained an EMBO fellowship for a postdoc to develop his own research line at the PSB department of the VIB in Ghent. This new research line is focused the molecular regulation of developmentally controlled programmed cell death during plant reproduction. Shortly afterwards, he was nominated Junior Group Leader on the same research topic and is currently leading a group of seven researchers.

Simon Stael, Researcher at the **Flemish Institute for Biotechnology (VIB)**, Ghent, Belgium

Simon Stael started his studies at the University of Ghent, Belgium, and finished his Master's thesis in Turku, Finland, at the lab of Dr. Eva-Mari Aro. This kick-started his interest in stress acclimation in plants. Thereafter, he did a PhD thesis in Vienna, Austria, on the 'Discovery of organellar calcium signaling components in *Arabidopsis thaliana*' in the Marie-Curie Initial Training Network 'COSI' (Chloroplast Signals) under the supervision of Dr. Markus Teige. Now he is back in Ghent for some more discoveries with a focus on metacaspase substrate proteins, with the aim to modulate programmed cell death in *Arabidopsis thaliana* during pathogen stress. This project is shared between the groups of Dr. Kris Gevaert (VIB Department of Medical Protein Research) and Dr. Frank Van Breusegem (VIB Department of Plant Systems Biology).

INVITED SPEAKERS

Wednesday, October, 2nd, 2013

Renier van der Hoorn, Research group leader at **Max Planck Institute** for Plant Breeding Research, Munchen, Germany

Renier van der Hoorn studied chemistry at Leiden University, focused on plant molecular biology and biochemistry. After his graduation in 1996, he started his PhD in Molecular Phytopathology at Wageningen University (Wageningen NL), working on tomato resistance proteins. After finishing his PhD studies in 2001, he worked for one year at the Sainsbury lab (John Innes Centre, Norwich, UK) and started his own research program by introducing and applying activity-based protein profiling in plants. He initiated the Plant Chemetics lab in October 2005 at the Max Planck Institute of Cologne and will soon continue his research program at the Plant Science Department of the University of Oxford, UK.

Evolution of Secreted immune Proteases and Their inhibitors

The leaf apoplast is an ancient battleground in plant-pathogen interactions. This is the compartment where most pathogens reside and from which they manipulate the host. Surprisingly, despite the importance of molecular events in the apoplast during infection, little is known about host-pathogen interactions in this compartment. I will introduce this topic with the role of secreted cysteine proteases of tomato. Pathogens from various kingdoms (fungi, oomycetes, bacteria and even nematodes) secrete structurally unrelated small proteins that specifically inhibit these defence-related proteases. The proteases are under diversifying selection and different variant residues affect different protease-inhibitor interactions. Tomato plants with reduced protease levels are hypersusceptible for various pathognes, confirming a role of these proteases in immunity. Besides proteases, plants also secrete a broad variety of other hydrolytic enzymes during immune responses. Our research program aims at the detection of their activities during immune respopnses and infection using activity-based proteomics. Several secreted hydrolases show differential activity upon infection of Nicotiana benthamiana by Pseudomonas syringae, and many of these differential activities do not correlate with protein levels, suggesting that they are manipulated by the pathogen in the apoplast. These studies indicate that molecular antagonistic interactions in the apoplast are common but poorly understood.

Robert Fluhr, Head of a research lab in the Department of Plant Sciences and the Department for Biological Services in **Weizmann Institute of Science**, Rehovot, Israel

Robert Fluhr is head of a research lab in the department of Plant Sciences in the Weizmann Institute of Science (http://www.weizmann.ac.il/plants/fluhr/). In addition to this activity he heads the Department for Biological Services in the Institute (http://bioservices.weizmann.ac.il). Plants respond rapidly to defend themselves from multiple environmental insults that include abiotic and biotic challenges. One common manifestation of plant defense is programmed cell death (PCD). Prof Fluhr's main interests are in understanding the control of cell death in relation to reactive oxygen species (ROS) and proteases. His lab has conducted research in stress promoted ROS produced by NADPH oxidases, aldehyde oxidases, quinone reductases or by organelles and has helped set up a bioinformatics platform to identify the expression of ROS species (app.agri.gov.il/noa/ROSMETER.php). In work on proteases, the group has shown the conserved features of an important group of plant protease inhibitors, serpins and their role in controlling vacuolar cell death.

Serpins Control Cell-death Proteases During Biotic and Abiotic Stress

Features of programmed cell death (PCD) such as cell shrinkage and DNA fragmentation are common to animals and plants; yet, the molecular signaling components initiating PCD differ. Less is known about the possibility of shared mechanisms in the final execution steps of PCD. Serpins are an important group of proteinase inhibitors that uniquely curb the activity of proteases by irreversible inhibition; however, their role in plants remains obscure. We show that during plant cell death initiated by necrotrophic interactions, AtSerpin1, present in the cytoplasm exhibits prosurvival function by inhibiting its target pro-death vacuolar protease, RD21. Elicitors of PCD like BTH and oxalic acid, stimulated changes in vacuole permeability that resulted in concomitant formation of a covalent AtSerpin1-RD21 complex. Mutant plants lacking RD21 or plants with AtSerpin1 overexpression exhibited significantly less elicitor-stimulated PCD than plants lacking AtSerpin1. Reactive oxygen species are pervasive intermediates that appear to play a role in the signaling process which lead to vacuolar-mediated cell death. Thus, a degree of commonalty exists between animal and plant execution of certain types of PCD where a serpin controls the pro-death functions of compartmentalized proteases by determining a set-point for their activity.

Patrick Gallois, Executive Director Operations, **EPCC**, University of Edinburgh, UK

Patrick Gallois received his PhD in Plant Development from the University of Burgundy, France, which was followed by a four-year post-doctoral fellowship in the Plant Biochemistry Department at Rothamsted Experimental Station, UK. This led to a permanent position at the University of Perpignan in the Laboratoire Génome et Développement des Plantes, CNRS UMR 5096 of Dr. Delseny. Since 2000, Patrick Gallois has been a member of staff at the Faculty of Life Sciences of the University of Manchester, UK. His lab focuses on the regulation of Programmed Cell Death using Arabidopsis and with a particular attention to the role of proteases. Member of the French National University Council (CNU)- Plant and Animal Physiology Committee-1999-2003.

Protease interactions Regulating ER-stress induced PCD in *Arabidopsis*

A prolonged Endoplasmic Reticulum (ER) stress can induce Programmed Cell Death (PCD) in plants and ER stress-induced PCD is relevant to plant responses to biotic and abiotic stresses. For example, ER stress was shown to mediate drought-induced PCD in Arabidopsis roots. In addition, ER stress-induced PCD facilitated mutualistic fungus Piriformospora Indica colonization in Arabidopsis root. However, there is no detailed molecular mechanism yet to connect ER stress and PCD. Several plants proteases are key players in plant PCD regulation. We investigated the relative contribution of proteases including VPE, cathepsin B and proteasome in ER stress-induced PCD. By analyzing the PCD phenotypes using cathepsin B knockout lines and proteasome specific inhibitors, we found that cathepsin B positively regulate ER stress-induced PCD, while proteasome negatively regulate ER stress-induced PCD. Further investigations indicated that protease inhibitors could switch ER stress-induced PCD from a vacuolar cell death to a necrotic cell death.

Kris Gevaert, Director of the Department of Medical Protein Research, **VIB, Ghent Univeristy**, Ghent, Belgium

Gevaert obtained his PhD in Biotechnology in 2000 at Ghent University (Belgium). He was a post-doctoral fellow with the Fund for Scientific Research (Flanders, Belgium) until 2006 and got appointed Professor in Functional Proteomics at Ghent University in 2004. Since 2005 he heads the Functional Proteomics group of the VIB Department of Medical Protein Research and also the VIB Proteomics Expertise Centre which is part of the FP7-funded PRIME-XS research infrastructures consortium. In 2010 he got appointed Full Professor at Ghent University and is currently acting director of the VIB Department of Medical Protein Research. Together with Joël Vandekerckhove he has introduced the suite of COFRADIC proteomics technologies which his group applies to the deep analysis of protein modifications, including protein processing by proteases. Further, the COFRADIC platform was the basis for establishing the VIB/UGhent spin-off company Pronota that focuses on protein biomarkers for various human diseases. His group published more than 180 papers and several book chapters on the development and applications of proteomics techniques in several areas of biomedical and life sciences research.

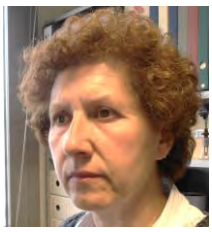
Positional Proteomics Approaches for Protease Degradomics

Proteases polish proteomes after activating or inactivating their substrates. Proteomic approaches for studying protease substrates aged over the past decade and now allow for detailed characterizations of protease degradomes. Our lab developed positional proteomics approaches that enrich for the novel protein termini that are generated upon protein processing by proteases. I will here discuss our latest developments which include strategies to distinguish efficiently processed substrates from inefficiently cleaved ones, more automated identification of protease substrates and the identification of carboxypeptidase substrates and characterization of their specificities using natural peptide libraries.

Frank Van Breusegem, Professor at **Ghent University** and Researcher at the **Flemish Institute for Biotechnology (VIB)**, Ghent, Belgium

(See his CV at the Scientific Committee Section)

Metacaspase Degradomics



Isabel Díaz, Full Professor at Centro de Biotecnología y Genómica de Plantas, **Universidad Politécnica de Madrid,** Madrid, Spain

PhD and Master's in Plant Biology by Universidad Complutense de Madrid. Postdoctoral Research Contract (1989-1993) CNB-CSIC/UPM. Scientific Researcher and group leader (2008-present) CBGPUPM-INIA. Full Professor (2012-present) Biotechnology Dept. Agronomy, UPM. Research Fellow at Planck-Institut für Züchtungsforchung, Cologne Germany. Research Fellow at Dept Botany, University of Nottingham UK. Visitant Professor Plant Cell Molecular Biology Laboratory, University of Florida, Gainesville, Florida, USA. Dr. Díaz has more than 60 articles published in SCI journals and 11 book chapters of international editorials. Editorial Board of Transgenic Research (Springer Editorial, The Netherlands). Associate coordinator to ANEP Ministry of Economy and Innovation, Spain. Reviewer of scientific articles of more than 25 different journals. Reviewer of research projects of Spanish and international institutions. Supervisor of 7 PhD thesis, 6 Master thesis and 8 Degree thesis.

Potential Biotech Applications of Cysteine-proteases and Their Inhibitors

Proteases occupy the most relevant position among industrial enzymes, representing near 60% of all commercialized enzymes in the world. However, the number of proteases from plant origin used in industrial processes is low. Probably, the most frequently plant proteases employed in a variety of industrial processes are papain, bromelain and ficin, belonging all of them to cysteine-protease class. They are considered traditional enzymes in the industry but they are still focus of attention from the pharmaceutical and biotechnology industries because of their strong proteolytic activity on a wide variety of substrates and because they are active over a range of temperatures and pHs. Besides, plant protease activities are regulated by protease inhibitors, small plant proteins with a wide range of applications in industry. The recent biotechnological developments and particularly, protein engineering, predict a big future for plant proteases and their inhibitors with improved industrial properties. Here, it is presented the whole family of cysteine-protease C1A from barley and their inhibitors, the cystatins. A revision on their potential roles in different physiological events in the plant, are also mentioned and their potential application as proteins with multiple roles for controlling plant development and plant responses to abiotic and biotic stresses.

Peter Bozhkov, Department of Plant Biology and Forest Genetics, **Uppsala BioCenter**, Swedish University of Agricultural Sciences and **Linnean Center for Plant Biology**, Uppsala, Sweden

Peter Bozhkov received his PhD degree in Plant Physiology in 1994 at the St. Petersburg Botanical Institute. He pursued his postdoctoral studies at the Swedish University of Agricultural Sciences in Uppsala, where he has established his own laboratory in 2005. At present Dr. Bozhkov is a member of the faculty at the same university and also a group leader at Uppsala BioCentre. His group is studying mechanisms of programmed cell death and autophagy in plants.

Cell-autonomous and Organismal Roles of Autophagy in Plant Development

Animals have evolved sophisticated machinery to remove apoptotic bodies and clean up necrotic debris for damping inflammatory response. Plants appear more pragmatic, as they utilize dying cells and cell corpses to construct their bodies, as well as to store and transport nutrients, growth factors, and secondary metabolites. The presence of rigid cell walls and the absence of phagocytosis permit cell corpses to stay post-mortem for a very long time. Disassembly of plant cells during developmental programmed cell death (PCD) is likewise a slow process, which can take up to several days. This mode of PCD is reliant on the gradual engulfment of the cytoplasm by the lytic vacuoles and is hence called vacuolar cell death. We have found that autophagy – a major cellular catabolic process - plays a central role in the execution of vacuolar cell death in the Norway spruce embryo-suspensors. The role of autophagy is cell-autonomous, since down-regulation of ATG genes specifically in the suspensor cells acts as a switch from vacuolar cell death to necrosis, which impairs embryonic patterning and leads to developmental arrest. It has become well known in the last few years that yeasts, worms, flies and mammals with enhanced level of basal autophagy live longer, whereas suppression of autophagy results in premature death or shortened lifespan. Current studies in my laboratory establish autophagy as an important process in the control of plant phenology and longevity. We have found that changes in the expression of some ATG genes can modulate autophagic flux in the leaves of Arabidopsis, which in turn affects phenology and lifespan of the plants. Interestingly, manipulation of both autophagic flux and organismal lifespan can also be achieved in wild type Columbia plants by changing their caloric status through increasing or decreasing light intensity.

Hanele Tuominen, Senior lecturer at the Plant Physiology Department, **Umeå Universitet**, Umeå, Sweden

Hannele Tuominen received a PhD at the Swedish University for Agricultural Sciences in Umeå, Sweden and is, after a post doc period at the Insitute of Biotechnology in the University of Helsinki in Finland, active as an associate professor at Umeå Plant Science Centre (UPSC) in Umeå, Sweden. She has a long-term interest in wood formation in forests trees and in the herbaceous model system Arabidopsis thaliana that also makes quite a bit of "wood" especially in the hypocotyl after a couple of months' growth period. Her current research focuses on cell death in xylem elements and how this impacts on wood properties and biomass production of forest trees. Current interests include comparative studies between different developmental cell death processes in Arabidopsis and the analysis of xylem cell death in a new model organism, the Norway spruce.

Post Mortem Program During Developmental Cell Death in *Arabidopsis*

Xylem cell death is required for proper function of the vessel elements in water transport. We have identified Arabidopsis thaliana METACASPASE9 (AtMC9) as a putative regulator of vessel cell death. Reverse genetic analysis of AtMC9 T-DNA knock-out lines showed normal progression of protoxylem vessel cell death in roots of young seedlings. However, detailed electron microscopic analysis of the mutant revealed a delay in post-mortem clearance of the protoxylem vessel elements, supporting a role for AtMC9 in autolytic processes during vessel cell death. Localization of the AtMC9 protein in cytoplasmic aggregates of the late maturing vessel elements and the effect of AtMC9 on both stability and activities of vacuolar localized papain-like cysteine proteases (PLCPs) supported this conclusion. Additional insight was obtained in newly established Arabidopsis tracheary element (TE) cell cultures, where almost complete suppression of AtMC9 expression in several transgenic RNAi lines resulted in altered cysteine protease activities and increased presence of undegraded acidic bodies in the vacuole during TE differentiation. We propose therefore that AtMC9 is part of a control mechanism which guarantees, in living TEs, degradation of acidic bodies of the vacuole and, in dead TEs, complete degradation of the vessel cell contents by activating unknown PLCPs. We also present results on an upstream regulatory mechanism of AtMC9 function, and finally propose function of AtMC9 and related hydrolytic enzymes in another developmental context

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Veronica Franklin-Tong, **University of Birmingham**, School of Biosciences, Birmingham, United Kingdom

Noni Franklin-Tong's research focuses on the cellular mechanisms involved in the model cell-cell recognition system of self-incompatibility (SI) in *Papaver rhoeas* (the Field Poppy). She has made major contributions to the field of self-incompatibility, a field that has high importance in relation to the future focus on food security. Her research has had a world-wide impact in the broader fields of plant cell signalling, the plant cytoskeleton and programmed cell death in plants. Her work includes several publications in *Nature*, has been highlighted in *News & Views* and *"Editor's Choice" in Nature and in "Leading Edge" in Cell*. Noni is currently Secretary General for the International Association of Sexual Plant Reproduction Research (IASPRR). She is currently on the Editorial Board of *Journal of Experimental Botany*, and *Plant Reproduction*, and is a Review Editor for *Frontiers in Plant Physiology*. Noni has a long-term commitment to enthusing children about science education and has been involved in providing the general public with a broader understanding of science through a number of activities. She was one of the original BBSRC Regional Coordinators of the Schools Liaison Scheme.

Integrating the Signalling Networks That Trigger Programmed Cell Death in Self-incompatible *Papaver* Pollen

Self-incompatibility (SI) is a genetically-controlled mechanism used by many angiosperms to prevent self-fertilization and inbreeding. A multi-allelic S locus allows discrimination between "self" (incompatible) pollen from "non-self" pollen on the stigma. Interaction of matching pollen and pistil S-determinants allows "self" recognition and triggers rejection of incompatible pollen. The S-determinants for Papaver rhoeas (poppy) are PrsS and PrpS. PrsS is a small novel protein that acts as a signalling ligand that interacts with its cognate pollen S-determinant PrpS, a small novel transmembrane protein. Interaction of PrsS with incompatible pollen stimulates increases in cytosolic free Ca2+ and influx of Ca2+ and K+. ROS and NO signals are also implicated. Downstream targets include the cytoskeleton, a soluble inorganic pyrophosphatase, and a MAP kinase, PrMPK9. The major focus for SI signals is initiation of programmed cell death (PCD). I will provide an overview of our understanding of how PCD in this system operates, focusing on how the signals and components are integrated. I will also discuss our recent functional expression of PrpS in Arabidopsis thaliana pollen.

Moritz Nowack, Researcher at the **Flemish Institute for Biotechnology (VIB)**, Ghent, Belgium

(See his CV at the Scientific Committee Section)

The Troublesome Transition: Programmed Cell Death During Plant Reproduction

Programmed cell death (PCD) is an essential function of an organism's development and its interaction with the environment. In animals, various forms of PCD have been studied intensively, and molecular mechanisms controlling some PCD forms, apoptosis for instance, are known in great detail. By contrast, still little is known about the regulation of PCD in plants, though its importance in plant development and immunity is without controversy. In our lab at the PSB department of VIB, we are investigating developmentally controlled PCD with an emphasis on plant reproduction. Many processes during gamete production, fertilization and seed development include PCD – indeed, reproductive success and seed set greatly depend on timely execution or prevention of PCD. I will give an overview over our research concept and will present the latest results aiming to uncover molecular pathways that control onset and execution of PCD in plant development.

Christiane Funk, Professor in Biochemistry at **Umeå Univesity**, Umeå, Sweden

Christiane Funk is Professor in Biochemistry at Umeå University, situated in Northern Sweden. She is associated with the Umeå Plant Science Centre, an organization of more than 30 different research groups focusing on various aspects of plant science. With her research team she is studying the model plant *Arabidopsis thaliana*, the cryptophyte algae *Guillardia theta* and the cyanobacterium *Synechocystis sp.* PCC 6803 to study the assembly and degradation pigment-binding proteins. After her Ph.D. at the TU Berlin, Germany, Christiane Funk performed post-doctoral research stays in the groups of Prof. Wim Vermaas, Arizona State University, USA and Prof. Tom Wydrzynksi, Australian National University, Australia. She then builds up her own research group at Stockholm University, Sweden and in 2002 moved to Umeå.

Impact of Deletion of the Metalloprotease FtsH11 in *Arabidopsis thaliana*

Proteolysis is of tremendous importance for plants, leaf senescence and seed germination are two examples where proteolysis, together with storage carbohydrate degradation, is the main driver of the whole process. Yet, knowledge about plant proteolysis is very incomplete and scattered. The FtsH proteases are a family of ATP-dependent metalloproteases. FtsH proteases are found in eubacteria, animals and plants and given their prokaryotic evolutionary origin, it is not surprising that their subcellular localization is restricted to mitochondria and chloroplasts. In *Arabidopsis thaliana* 12 active family members are present, in addition, five genes coding for proteins homologous to FtsH (AtFtsHi 1-5) have been detected in the genome, which lack the conserved zinc-binding motif HEXXH, and therefore presumably are inactive. Of the 12 active FtsH poteases, eight FtsH proteins (FtsH1, 2, 5, 6-9, 12) are transported into the chloroplast and three into mitochondria (FtsH3, 4, and 10). FtsH11 is reported to be dual targeted, it has been found in mitochondria by proteomic analysis, and GFP fused to the pre-sequence of FtsH11 was targeted to the chloroplast. Here we will discuss the impact of FtsH11 during plant development.

Zoe Wilson, Professor of Developmental Plant Biology at **The University of Nottingham**, UK

Zoe Wilson's research interests include the molecular genetic analysis of floral development and male reproduction, focusing specifically on pollen and anther development. The aim of this is to improve crop yields by developing effective breeding strategies and by optimizing/controlling pollen fertility. She has used male sterile mutants that are defective at various stages of pollen formation to study the physiological and molecular basis of anther and pollen development, and also the effects of abiotic and biotic stress and plant hormones upon fertility. One particular area of focus has been the role of the tapetum in pollen wall development and the breakdown of this tissue, via programmed cell death, for functional pollen production. In this work she is using Systems Biology and Bioinformatic Approaches to construct, develop and functionally test pollen/anther regulatory networks in model systems and then translating these to crops of economic value.

Tapetal Cell Death. The Way to Pollen Fertility

The development of viable pollen involves a number of key stages and interactions between different cell types within the anther. The tapetum tissue is critical in this process; it is the innermost layer in the anther, which is involved in the biosynthesis and secretion of pollen wall materials. This tissue goes through a developmental progression, which culminates in programmed cell death (PCD). Alterations to this PCD pathway result in a breakdown of pollen and male sterility. Many transcription factors have now been identified that alter tapetal PCD in both Arabidopsis and rice; despite acting at different stages and causing subtly different phenotypic changes to the tapetum they all result in alterations to tapetal PCD, and when mutated result in a failure of pollen development and male sterility. The regulatory pathway of some of these transcription factors will be discussed alongside the use of different markers to follow the process of PCD in the tapetum.

Stephan Hoth, Full Professor at the University of Hamburg and Head of Molecular Plant Physiology at the Biocenter Klein Flottbek, **University of Hamburg**, Germany

Stephan Hoth is a Professor at the University of Hamburg and he is also the head of Molecular Plant Physiology at the Biocenter Klein Flottbek, University of Hamburg, since 2011. After his Ph,D. at the Universities of Hannover (Biophysics Institute) and Würzburg (Julius-von-Sachs-Institute), Germany, Stephan Hoth performed post-doctoral research stays in the groups of Prof. Dr. R. Hedrich at the Julius-von-Sachs-Institute, University of Würzburg, Germany, and Prof. Nam-Hai Chua, at Rockefeller University, New York, USA. Between 2002 and 2011 he was a group leader at the Department Biology, Molecular Plant Physiology, Friedrich-Alexander-University Erlangen-Nürnberg, Germany. In 2008 he achieved Habilitation in Molecular Plant Physiology at the Faculty of Natural Sciences of the Friedrich-Alexander-University Erlangen-Nürnberg, Germany.

The Ubiquitin Ligase Mutant *saul1* – an Inducible Model System for Developmental Cell Death

Senescence and cell death are well defined and highly regulated developmental processes that guarantee optimal growth and reproduction of plants. To study these important processes, suitable model systems are required. In Arabidopsis mutants that lack expression of the *SAUL1* gene (*SENESCENCE ASSOCIATED UBIQUITIN LIGASE 1*) both processes, senescence and cell death, are inducible at any developmental stage by transfer to low light conditions. Hence, these mutants represent an optimal model system to investigate the molecular basis for regulation of senescence and cell death. SAUL1 is a plasma membrane-associated plant U-box armadillo repeat ubiquitin ligase, which suppresses senescence and cell death in wild type plants. In *saul1* mutant plants, low light treatment results in accumulation of salicylic acid (SA), and a series of microarray experiments showed that SA and defense genes are most rapidly induced. Among these genes was *PAD4* that is important for SA signal potentiation. The presence of *PAD4* is absolutely required for *saul1* phenotypes as the *saul1/pad4* double mutant acts like wild type. By applying molecular genetics, biochemistry, bioimaging, and molecular physiology we use the *saul1* model system to study the molecular mechanisms regulating senescence and cell death.

INVITED SPEAKERS

Thursday, October, 3rd, 2013

Sophien Kamoun, Head, **The Sainsbury Laboratory, John Innes Centre,** Norwich Research Park, UK

Sophien Kamoun joined The Sainsbury Laboratory in 2007 and rose to Head of Laboratory in 2009. He also holds the rank of Professor of Biology at The University of East Anglia. Prof. Kamoun received his B.S. degree from Pierre and Marie Curie University, Paris, France, and his Ph.D. in Genetics from the University of California at Davis in 1991. He then was a postdoctoral fellow at the NSF Center for Engineering Plants for Resistance Against Pathogens, UC Davis, and at the Department of Phytopathology, Wageningen University, Netherlands. From 1998-2007, Prof. Kamoun carried out research on oomycete molecular genetics on the faculty at the Ohio State University, Department of Plant Pathology, Wooster campus. At The Sainsbury Laboratory, Prof. Kamoun continues to exploit genomics resources to improve understanding of plant pathosystems, unravel novel processes and concepts in plant-microbe interactions, and devise original disease management strategies based on the gained knowledge. Throughout his career, Prof. Kamoun has made unique and ground-breaking contributions to understanding plant-parasite interactions. His work on oomycete effector biology and pathogenomics has resulted in new approaches to breeding disease resistant crops.

Effector Specialization Following a Host Jump in the Irish Potato Famine Pathogen Lineage

Accelerated gene evolution is a hallmark of pathogen adaptation following a host jump. However, the biochemical basis of adaptation and specialization to new hosts remains largely unknown. Here, we describe functional specialization of a plant pathogen effector following a host jump. Orthologous protease inhibitor effectors from the Irish potato famine pathogen Phytophthora infestans and its sister species Phytophthora mirabilis are better adapted to protease targets from their respective host plants potato and Mirabilis jalapa. Single amino acid polymorphisms in the inhibitors and their target proteases largely underpin biochemical specialization. These results provide a molecular framework for how antagonistic pleiotropy drives effector specialization in a plant pathogen ultimately resulting in diversification and speciation.

Gunther Doehlemann, Research Group Leader at **Max Planck Institute** for Terrestrial Microbiology, Marburg, Germany

Gunther Doehlemann received a Ph.D. at University of Kaiserslautern, Germany, in 2006. Then he performed post-doctoral research in Max Planck Institute (MPI) for Terrestral Microbiology. After a Short Term Fellowship at European Molecular Biology Organization at Stanford University (Walbot Lab), he became a group leader in MPI for Terrestrial Microbiology. He achieved Habilitation in Genetics at Philipps-Universität, Marburg, in May 2012. Gutnher Doehlemann is Privat dozent at Philipps-Universität, in Marburg, since October 2012.

Modulation of Apoplastic Immunity in the *Ustilago maydis* – Maize Interaction

The smut fungus *Ustilago maydis* causes the formation plant tumors on all aerial organs of its host plant maize. *U. maydis* establishes a biotrophic interaction directly upon host penetration and growth intra- as well as intercellularly without eliciting visible defense reactions. This biotrophic lifestyle requires an efficient suppression of plant defense responses. Effector proteins, which are secreted by the biotrophic hyphae are considered to be instrumental for the modulation of host immunity. However, so far only little is known about the molecular functions of individual effector proteins. Our recent findings suggest that conserved components of the apoplastic plant defense machinery are direct targets of *U. maydis* effectors. This particularly involves papain-like cysteine proteases, which are crucial for the activation of salicylic-acid dependent defense reactions in maize. We now show that a set of cysteine proteases is inhibited both by a *U. maydis*-induced maize cystatin as well as by the secreted effector Pit2, and both these factors are essential for compatibility. Molecular analysis of Pit2 also identified a conserved sequence motif, which acts as a novel type of plant cysteine protease inhibitors that is essential for fungal virulence. Together, the presented data provide new insights on the suppression of apoplastic immunity by a biotrophic fungal pathogen.

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Pierre De Wit, Laboratory of Phytopathology, **Wageningen University**, Wageningen, The Netherlands

Pierre De Wit received his PhD at Wageningen University studying the pathosystem *Cladosporium fulvum*-tomato. After his PhD he did spend a sabbatical year in the USA at the department of Phytopathology of KSU, Lexington Kentucky, USA. In 1982 he became assistant, professor at the Laboratory of Phytopathology of Wageningen University, associate professor in 1986 and full professor and head of the Laboratory in 1990. His research is focused on fungal effectors from *C. fulvum* and related Dothideomycete fungi like *Mycospaerella fijiensis* and *Dothistroma septosporum,* and effector-triggered immunity responses in tomato and tobacco. His group discovered the biological functions of several fungal effectors, including Avr2, a cysteine protease inhibitor, and Avr4, a chitin-binding protein that also induced Cf-2 and Cf-4-mediated hypersensitive responses, respectively. Recently, he discovered effectors with enzymatic functions including a-tomatinase and endo-arabinase. In 1999 he became member of the Royal Netherlands Academy of Sciences and in 2008 he became Royal Netherlands Academy Professor. Pierre de Wit received the Noel T. Keen award and the Emile Christian Hansen award for his his pioneering work on fungal effectors.

The Role of Plant and Fungal proteases in the Pathosystem *Cladosporium fulvum*-tomato

The tomato pathogen *Cladosporium fulvum* is a biotroph that secretes multiple effectors in the apoplast of its host plant during infection. One of them is a cysteine protease inhibitor, Avr2, that interacts with cysteine-protease Rcr3 and triggers Cf-2-dependent defense responses including a hypersensitive response. Rcr3 is guarded by the Cf-2 resistance protein. The Cf-2 protein also mediates disease resistance to the pathogenic root nematode *Globodera rostochiensis*. The Cf-2-mediated nematode resistance is triggered by the venom allergen-like effector protein, Gr-VAP1,that is secreted by *G. rostochiensis* and perturbs Rcr3. Interaction of both fungal Avr2 and nematode Gr-VAP1 with Rcr3 from Solanum pimpinellifolium (pim) triggers a Cf-2-mediated hypersensitive response. In the absence of Cf-2, Rcr3 increases susceptibility of tomato plants to *G. rostochiensis*, thus showing its role as a virulence target. Monitoring of host proteins like Rcr3 targeted by multiple pathogens broadens the spectrum of disease resistances mediated by single resistance genes like Cf-2. *C. fulvum* also secretes chitin-binding proteins like Avr4 and Ecp6, of which the first protects fungi against the deleterious effects of plant chitinases and the second scavenges chitin fragments preventing them from eliciting chitin receptor-mediated basal defense. Recently, we found evidence that plant pathogenic fungi also secrete protease that can inactivate chitinases by removing their chitin-binding domains. This might be the last line of defense in case the first two are not sufficient. The discovery of a novel effector Avr5, a pattern-associated molecular pattern, an endo-arabinase, and an exoglucanase releasing a damage-associated molecular pattern will alsobe briefly discussed.

Nuria Sànchez-Coll, Resercher at the **Center for Research in Agricultural Genomics (CRAG)** Barcelona, Spain

(See her CV at the Scientific Committee Section)

Metacaspase Complexes Regulating HR cell Death

We use an orthogonal approach to study deathosome dynamics during the hypersensitive response (HR) cell death a plant-specific localized immune response to pathogen recognition. In this context, we propose that the core members of the decision-making deathosomes are a limited set of proteins defined by the presence of an LSD1-like zinc finger domain, most of which have a key role in HR cell death regulation. These include two type I metacaspases, which we have recently shown to antagonistically regulate this process, suggesting an ancient link between cell death control and innate immunity in plants and animals. We have been able to identify native AtMC1-containing supramolecular complexes using gel filtration chromatography. In order to study their composition we have developed a novel technique to immunoisolate native protein complexes in planta. In a set of pilot experiments using this method, we have identified components of the AtMC1 deathosome, which dynamically respond to PCD triggers and may be part of a regulatory network. Among the AtMC1-interactors we have identified several cell death and disease resistance regulators and putative metacaspase substrates

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Susana Rivas, Director of Research, **CNRS,** LIPM, Toulouse, France

Susana Rivas received her Ph.D. in University of the Basque Country in 1997. After her post-doctoral stay at The Sainsbury Laboratory, Norwich (UK), she became First Class Researcher in the Laboratoire des Interactions Plantes-Microorganismes (LIPM), in the French National Centre for Scientific Research (CNRS). And Susana Rivas is CNRS Director of Research in LIPM from 2012.

Transcriptional Control of *Arabidopsis hypersensitive* Cell Death in Response to Bacterial Pathogens

Plant defense responses are often associated to the development of the so-called hypersensitive response (HR), a form of programmed cell death that prevents spreading of the pathogen beyond the inoculated zone. This defense-associated cell death is closely connected to plant physiological and developmental processes and needs to be tightly regulated to be not only efficient but also beneficial to the plant. Moreover, the sharp boundary of the HR suggests the existence of efficient mechanisms that control cell death and survival. Transcriptional regulation in host cells plays a crucial role in the establishment of plant disease resistance to pathogen attack. The MYB transcription factor MYB30 is a positive regulator of Arabidopsis defense and HR responses to bacterial pathogens. MYB30 appears to modulate cell death-related lipid signaling by enhancing the synthesis of sphingolipid-containing very long chain fatty acids (VLCFAs) after bacterial inoculation. Plant and animal pathogenic bacteria inject type III effectors (T3Es) into host cells to suppress host immunity and promote successful infection. We have shown that MYB30 is targeted by the bacterial T3E XopD, resulting in suppression of MYB30-mediated plant defenses and underlining the crucial role played by MYB30 in the regulation of plant disease resistance. In addition, the activity of MYB30 is tightly controlled inside plant cells. The spatiotemporal control of MYB30-mediated HR responses through different regulators (including the secreted phospholipase *Ats*PLA2-α, the RING-type E3-ubiquitin ligase MIEL1 and a serine-type endopeptidase that belongs to the Arabidopsis subtilase family) will be discussed.

Ikuko Hara-Nishimura, Professor at **Kyoto University**, Kyoto, Japan

Ikuko Hara-Nishimura received her Ph.D. in Osaka University. She was a research assistant in Natural Institute for Basic Biology between 1990 and 1997, and then became associate professor until 1999. Since 1999 Ikuko Hara-Nishimura is Professor at Kyoto University. She received the Japanese Society of Plant Physiologists Award in 2013, the Prize for Science and Technology and the Commendation for Science and Technology by MEXT in 2007, and the Chunichi Cultural Prize in 2006. She currently is member of Review Panel of MEXT (Government of Japan). She also was member of the Expert Panel on Basic Policy of Council for Science and Technology Policy at Cabinet Office (Government of Japan) between 2007 and 2011; the Review Panel of Ministry of Agriculture, Forestry and Fisheries and Research Council between 2005 and 2009, and the Review Panel at Council for Science and Technology Policy in 2007 and 2008.

Endomembrane Systems Responsible for Defense Strategies of Plants

Plant endomembranes including vacuoles and endoplasmic reticulum dynamically move and change their shapes within the cells. Previously, we reported that plants use vacuoles for cell autonomous plant immunity in two different ways. The first way involves fusion of vacuolar membrane and plasma membrane, which is triggered by the a virulent bacteria infection and allows vacuolar defense proteins to be discharged into the extracellular space where the bacteria proliferate. The fusion of vacuolar and plasma membranes is induced in a proteasome-dependent manner. The second way is associated with vacuolar membrane collapse followed by the release of vacuolar hydrolytic enzymes into the cytosol, resulting in rapid and direct cell death. This way is effective in the digestion of viruses proliferating in the cytosol. Intriguingly, both vacuole-mediated immune systems induce hypersensitive cell death by using caspase-like activities: caspase-3-like activity (DEVDase activity) of proteasome subunit PBA1 causes the membrane fusion, while caspases-1-like activity (YVADase activity) of VPE causes the vacuolar membrane collapse. In this meeting, we also touch on another ingenious two-compartment immune system, in which beta-glucosidases in the ER bodies of epidermal cells of roots and the vacuoles of myrosin cells of leaves are sequestered from their glucosinolate substrate. When cells are ruptured by herbivores, myrosinase converts the substrates into a toxic compound. These results provide an idea that plants use the vacuoles differently depending on the type of pathogenic organisms.

Morten Petersen, Associate Professor at the Department of Biology, **Copenhagen University**, Copenhagen

Morten Petersen obtained an MSc in Biology from U. Copenhagen on research he performed with Prof. Peter Ulvskov, then of the Danish Agronomic Institute of the Ministry of Agriculture on pod shatter in oil seed rape. He then obtained a PhD in 2001 from U. Copenhagen. His thesis work was carried out with Prof. John Mundy at the Institute of Molecular Biology, U. Copenhagen. His thesis research led to the discovery of the first MAP kinase knock-out in plants. His Post-Doctoral research focused on comparative studies of programmed cell death using post-genomic models including the plant Arabidopsis, the worm C. elegans, and humans. From 2003 Morten Petersen initiated work with C. elegans during visits to the group of Prof. Michael Hengartner (U. Zurich) and in 2005 he also initiated work with human cell cultures with the group of Professor Niels Ødum at Copenhagen University. During the following years he focused his research on autophagic cell death in plants. Since 2009 his research, as an Associate Professor at the Department of Biology, Copenhagen University, has focused on basal cell biological processes, including MAP kinase signalling in plant innate immunity and autophagic cell death in plants and animals. Apart from basal discoveries he has also focused on applied research. Currently, this includes ways to increase stress tolerance in crops and rapid production of cereals with increased resistance to microbial pathogens.

Pleiotropic Effects of Autophagy and NPR1 Deficiencies in Cell Death During Immune Responses and Development

Autophagy is a homeostatic degradation and recycling process that is also involved in defense against microbial pathogens and in certain forms of cellular suicide. Autophagy has been proposed to negatively regulate immunity associated cell death related to the hypersensitive response (HR), as older autophagy-deficient (atg) mutants are unable to contain this type of cell death 5-10 days after infection. Such propagating cell death was found to require Non-expressor of PR genes (NPR1), but did not occur in younger atg mutants. In contrast, we find that npr1 mutants are not impaired in rapid programmed cell death activation upon pathogen recognition. More importantly and for the first time, we provide molecular evidence that the NPR1 dependent spreading cell death in older atg mutants originates from an inability to cope with the excessive accumulation of ubiquitinated proteins and subsequent ER stress which derive from salicylic acid (SA)-dependent systemic acquired resistance (SAR). Thus, autophagy does not regulate cell death via a negative feedback loop through NPR1. Instead, npr1 loss-of-function indirectly rescues older atg mutants because atg npr1 double mutants are insensitive to SA and fail to induce SAR that would otherwise produce terminal stress in autophagy deficient cells.

Richard Vierstra, Professor of Genetics in **University of Wisconsin**, Madison, USA

Dr. Richard Vierstra earned his BS in biology and chemistry at the University of Connecticut in 1972, his Ph.D in plant biology from the DOE-Plant Research Laboratory at Michigan State University in 1980, and was a postdoctoral fellow with Dr. Peter Quail at the University of Wisconsin (1980-1983). He joined that faculty of the University of Wisconsin in 1984 and is currently the Stanley J. Peloquin Professor of Genetics. Rick was a Fulbright senior scholar at the University of Melbourne Australia (1993-1994). He served on the editorial boards of *Plant Physiology* and the *Journal of Biological Chemistry* and has been on numerous NIH, NSF, DOE and USDA study sections, including section chair for the USDA-NRICGP Plant Genetics Mechanisms program in 2001. Rick currently is a member of the Board and Treasurer for the International Society of Plant Molecular Biologists and on the Executive Committee for the American Society of Plant Biologists. Rick's research interests include: (1) mechanisms, regulation, and evolution of the ubiquitin/26S proteasome proteolytic system using *Arabidopsis* as the model; (2) roles of autophagy in plant growth development and survival under nutrient limitations; (3) functions of SUMOylation during the plant stress response; and (4) understanding the phytochrome signaling system in plants and microorganisms at the atomic level, using x-ray crystallography, NMR spectroscopy, and single particle EM. This work has resulted in almost 220 research publications, the training of 41 postdoctoral fellows, 25 Ph.D students and a host of undergraduates, and numerous awards including Fellow of AAAS (2002).

Functions and Regulation of ATG8-Mediated Autophagy in Plants

Autophagy-mediated turnover plays an essential role in cellular housekeeping by removing damaged organelles and unwanted cytoplasmic constituents, and is critical for plant defense and robust nutrient recycling, especially during nitrogen and fixed-carbon starvation. This 'self eating' is mediated by a conjugation system that modifies a pair of ubiquitin-like proteins ATG12 and ATG8 to eventually form an autophagic vesicle coated with the ATG8-phosphatidylethanolamine (PE) adduct. The ATG8-PE serves two purposes, one is to help direct the transport of autophagic vesicles to the vacuole for breakdown, and the other is to serve as a docking platform for a suite of ATG8-interacting proteins that selectively tether appropriate cargo within the vesicle lumen before enclosure. Using an extensive collection of *atg* mutants in *Arabidopsis*, we have characterized the pathway responsible for ATG8/12 conjugation and the kinase cascade that connects metabolic and environmental cues to the formation and transport of autophagic vesicles. A key regulatory step is controlled by the ATG1/13 kinase complex that works downstream of the TOR signaling system and ATG8/12 modification. It is not only necessary for vacuolar deposition of autophagic bodies but also becomes a substrate through the interaction of several subunits with ATG8, thus providing feedback control on autophagic turnover. In addition to bulk turnover, we found that the ATG system is responsible for the turnover of organelles like mitochondria and peroxisomes and large cytoplasmic complexes such as the 26S proteasome when dysfunctional or no longer needed. Proteasome turnover appears to be mediated by prior ubiquitylation of numerous core subunits. Using maize as a model, we have also begun to describe the roles of ATG8-mediated autophagy in crops. Our initial genetic studies revealed a key role in productivity by mobilizing nitrogen when limiting.

INVITED SPEAKERS

Friday, October, 4th, 2013

Guy Salvesen, Adjunct Professor of Pathology, UCSD. Program Director and Professor, **Sanford Burnham Medical Research Institute**, USA

Guy Salvesen earned his Ph.D. in biochemistry from Cambridge University and conducted postdoctoral research at the University of Georgia, USA, Strangeways Laboratory and MRC Laboratory of Molecular Biology in Cambridge. is Director of the Program in Apoptosis and Cell Death Research, Dean of the Graduate Program in Biomedical Sciences of Sanford-Burnham Medical Research Institute, Director of Scientific Training at Sanford-Burnham, and holds an Adjunct Professorship at the University of California, San Diego. He is on the editorial board of several journals, Vice Chair for the Americas and Reviews Editor of the Biochemical Journal, and Co-founder of the International Proteolysis Society.

Caspases and Paracaspases in Mammalian Cell Death and Survival Networks

Apoptosis is said to be dependent on caspases. But it has become pretty clear now that supposedly pro-apoptotic caspases can, paradoxically, also trigger non-apoptotic events. Moreover, the universe of caspase homologs includes proteases with distant relationship to caspases, which program entirely different cell signaling pathways. This talk will focus on the biochemical mechanisms that allow caspase-8 and its distant homolog (paracaspase) to program apoptotic cell death versus an opposing pathway to cell survival and clonal expansion in mammals.

Cristina Muñoz-Pinedo, Leader of the Cell Death Regulation Group at **IDIBELL**, Barcelona, Spain

Cristina Muñoz-Pinedo leads the Cell Death Regulation group at IDIBELL (Bellvitge Biomedical Research Institute) in Barcelona, Spain. She studied Biology in the University of Sevilla, and she started her scientific career in the field of cell death and cancer metabolism under the supervision of Dr. Abelardo López-Rivas at the CSIC, in Granada, Spain. After several short stays in international laboratories she received her PhD from the University of Granada in 2001. She then moved to San Diego to work under the supervision of Doug Green at the La Jolla Institute for Allergy and Immunology, where she studied the role of the mitochondria during cell death as an initiator of the apoptotic process and as a "victim" of caspase activation. After a short stay in St. Jude Children's Research Hospital, in 2006 she moved back to Spain to start a lab whose main interest is to understand why and how cells die when deprived of nutrients. Her lab is trying to apply this knowledge to improve treatment of cancer (to kill cancer cells with metabolic inhibitors) and stroke (to prevent ischemic cell death).

Necrosis, Typical and Atypical Apoptosis Induced by Glucose Deprivation in Cancer Cells. Role of Autophagy

Glucose depletion has been shown to kill tumor cells either by necrosis (non-apoptotic cell death) or by the mitochondrial pathway of apoptosis. We observed that several tumor cell lines of different origins die in a non-apoptotic manner when deprived of glucose. However, HeLa cells and mouse embryonic fibroblasts (MEF) died by apoptosis. Surprisingly, apoptosis was independent of the mitochondrial pathway, since it occurred in Bax, Bak-deficient MEF and in Bcl-xL-overexpressing HeLa cells. Apoptosis was mediated by caspase-8. However, neither the classical death receptor pathway nor the caspase-activating complex ripoptosome were involved in apoptosis. In response to nutrient shortage or organelle damage, cells undergo macroautophagy. Starvation of glucose, an essential nutrient, is thought to promote autophagy in mammalian cells. We thus aimed to determine the role of autophagy in cell death induced by glucose deprivation. Inhibition of autophagy by chemical or genetic means by using 3-methyladenine, chloroquine, a dominant negative form of ATG4B or silencing Beclin-1, Atg7 or p62 indicated that macroautophagy does not protect cells undergoing necrosis or apoptosis upon glucose deprivation. Moreover, glucose deprivation did not induce autophagic flux in any of the four cell lines analyzed, even though mTOR was inhibited. Indeed, glucose deprivation inhibited basal autophagic flux. In contrast, the glycolytic inhibitor 2-deoxyglucose induced pro-survival autophagy. Further analyses indicated that in the absence of glucose, autophagic flux induced by other stimuli is inhibited. These data suggest that the role of autophagy in response to nutrient starvation in animal cells should be reconsidered.

Karen McLuskey, Research Fellow at the Wellcome Trust Center for Parasitology, **University of Glasgow**, UK

Karen McLuskey studied Chemistry with Computer Applications at the University of Glasgow, where she was first introduced to X-ray crystallography. For her PhD she investigated the primary events bacterial photosynthesis, using membrane-protein crystallography, under the supervision of Profs. Neil Isaacs (crystallography) and Richard Cogdell (plant biochemistry). She completed two post-doctoral positions: the first with Prof. Wim Hol, University of Washington, Seattle and the second with Prof. Bill Hunter, University of Dundee, Scotland. Both of these posts involved using multi-disciplinary approaches involving X-ray crystallography, to investigate the structure/function relationships of proteins involved in the pathogenesis of disease caused by parasites. During this time she became interested in structure-based drug design and while in Dundee she was involved in the discovery of inhibitors for both Leishmania and Trypanosomes. Continuing with this type of work, she subsequently moved back to Glasgow University where she is currently working at the Wellcome Trust Centre for Parasitology with Prof. Jeremy Mottram, as a Research Fellow in structural biology.

Structural Insights into Why Metacaspases Are Not Caspases

The mammalian caspases (cysteine-dependent aspartate-specific protease)s are major regulators of apoptotic cell death pathways, proliferation and inflammation. Over a decade ago, metacapsases (and paracaspases) were discovered during a search for caspase orthologues in non-metazoan organisms. Notably absent in mammals, metacaspase sequences were identified in plants, yeast and parasitic protozoa and classified as part of the caspase structural family (Clan CD, Family C14 (MEROPS)). However, their substrate specificity and requirements for activation set them aside from the caspases: Caspases are Asp-specific functional dimers that are activated by dimerisation or by intra-chain cleavage, whereas metacaspases have Arg/Lys specificity, function as monomers, do not require processing for activity and are activated by calcium. Determining the X-ray crystal structure of a metacaspase from the protozoan parasite Trypanosoma brucei (TbMCA2) allowed the structural basis for these functional differences to be elucidated. It also allowed an in-depth analysis of the topological differences and similarities between, not only the caspases and metacaspases, but also the paracaspases and other available Clan CD family members, providing clear evidence that the metacaspases are structurally distinct from the caspases. In addition, biochemical and functional studies support the opinion that parasitic protozoa do not exhibit regulated cell death, demonstrating that trypanosome metacaspases are not caspases, after all.

Pierre Golstein, Centre d'Immunologie de Marseille-Luminy, **INSERM-CNRS-Université de la Méditerranée**, Marseille France

Pierre Goldstein, MD, PhD, trained at the Institut Pasteur, Paris, the Dept. of Tumor Biology (Pr. G. Klein) of the Karolinska Institutet, Stockholm, and the Tumor Immunology Unit (Pr. Mitchison) at University College London. He has been working at the Centre d'Immunologie INSERM-CNRS de Marseille-Luminy as a head of group for many years. He first studied mechanisms of T cell mediated cytotoxicity, demonstrated the existence of CTLA-1 and CTLA-3 (Granzymes B et A, respectively), in the perforin-granzyme pathway of cytotoxicity, and identified the Fas pathway of cytotoxicity, leading to the cloning of the Fas Ligand. This research also led to CTLA-4 and CTLA-8 (Interleukin-17), now studied by others in a therapeutic perspective. He then shifted to mechanisms of programmed cell death per se, studying first interdigital cell death in the mouse embryo, then focussing on developmental cell death in the protist Dictyostelium discoideum. Dictyostelium is an excellent genetically tractable model organism for the study of this death, which is being investigated as to its phenomenology and through genetic approaches as to its molecular bases.

Cell Death in *Dictyostelium*

Dictyostelium discoideum, a eukaryote, a protist, a slime mold, is unicellular in favorable conditions. It shows upon starvation multicellular development leading to fruiting bodies. Each of these fruiting bodies is made of a mass of spores on top of a stalk. This stalk is made of dying or dead cells. This cell death, developmental by definition, can be mimicked in vitro in cell monolayers allowing morphological study and genetic manipulations. Dictyostelium offers two main advantages for the study of this cell death. First, its genome, now sequenced, is small, compact, and haploid, favoring insertional mutagenesis. Second, from a cell death point of view this genome does not encode caspases or bcl-2 family members, thus in this model organism there is no apoptosis machinery that could interfere with the non-apoptotic cell death mechanisms at play. The results to be reported include a description of successive steps of this developmental cell death as mimicked in vitro (including paddle cell formation, rounding, vacuolization and cellulose shell formation), the induction and role(s) of autophagy in this cell death system, the requirement for this cell death of autophagy plus a qualitatively different second signal, a preliminary account of the general design of this cell death, corresponding signaling pathways with markers thereof including required molecules identified through insertional mutagenesis, and description of mitochondrial lesions.

Francesc Xavier Avilés, Director and full professor at the Dep. of Biochemistry and Molecular Biology of the **Universitat Autònoma de Barcelona** (UAB) and group leader at the **Institute for Biotechnology and Biomedicine** (IBB), Barcelona, Spain

Besides his activity at the UAB, where he got his PhD, he has been trained at the field of structural biology of proteins at the CSIC (Inst. Rocasolano, Madrid), University of Porstmouth (Biophysics Lab.), ETH-Zurich (Inst. Mol Biol & Biophys, Wüthrich Dpt.), Max-Planck Inst. Biochemie Munich (Huber Dpt.), University of Cambridge (Dept. Biochemistry), University of Uppsala (& BMC center) and University of Lund (Clinical Med. Dpt. & Grand Hosp.), with long or medium stays. There, also completed his training in bioinformatics and proteomics, as well as a further specialization on proteolytic enzymes and inhibitors. He supervised 39 PhD thesis, coauthored more than 230 peer-reviewed publications (H-index 39) and leaded a significant number of research projects and networks at the national and international levels. Also, has been member of the executive committees and coordinator of sections of scientific societies (such as SEBBM, SBE, SCB), and is member of editorial boards of international scientific journals, particularly in the fields of protein sciences and molecular-structural biology, protein production & modifications, and proteomics.

Strategies to Identify Ligands, Inhibitors and Natural Substrates of Carboxypeptidases and Other Proteolytic Enzymes

Protein-ligand, in general, and protease-ligand/-inhibitor/-substrate analytes and their interactions are subjects of great importance in structural and regulatory biology, proteomics and biotechnology-biomedicine at both fundamental and applicative levels. To investigate them it is convenient to select approaches which show high sensitivity, highthroughput and discriminative capability, in-vivo/ex-vivo monitoring and quantitativeness. Among these are mass spectrometry (MS) variants, and particularly the "Intensity-fading" strategy, which is fast and simple and has been developed by our group. We have preferentially applied it to crude and complex biological extracts, containing proteases and proteinaceous inhibitors of them, particularly those originated from invertebrates, species which constitute more than 95% of the animal phyla, quite challenging because very litle data is available for such systems at the genomics and biochemical levels. However, the strategy is fully applicable to other complex species, like vegetals. A somewhat related approach is MALDI.MS-Imaging (MALDI-MSI or MSI) which allows to visualize the distribution and fate of biomolecules in tissue sections. Proteins, peptides, lipids and metabolites can be analyzed in a selective and/or highthroughput manner. The application of MSI allows acquisition of protein and peptide profiles, biomarker discovery, biomarker localization, tissue classification or disease diagnosis and prognosis. In the present communication we shall describe some of our productive approaches and results in such fields. On the other hand, it will be discussed the development of synthetic inhibitors and inhibitory probes, based on peptide-phosphinic heads, the latter with a fluorescent head, to localize and track proteases in in-vivo models (cell cultures and tissues), enphasizing the nowadays growing importance of fluorescence in molecular imaging.

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OUTCOMES

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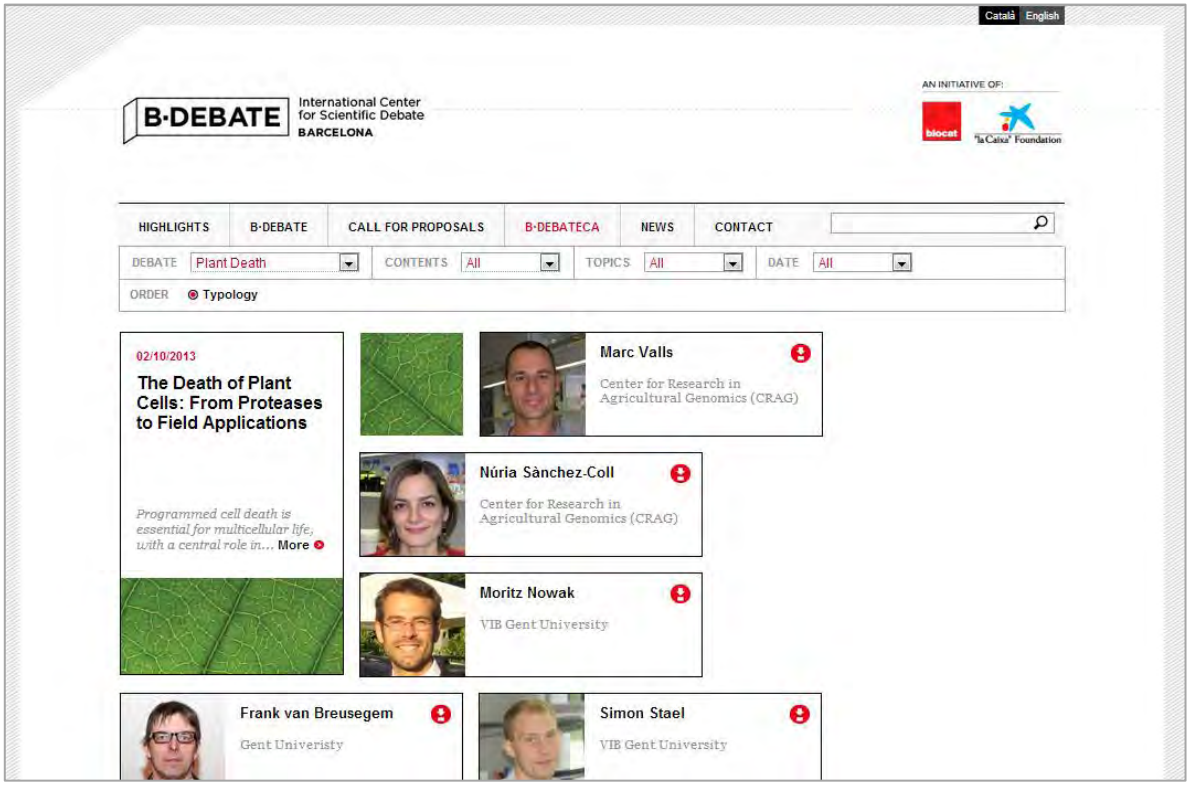

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Debates venue

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C/ Isaac Newton, 26 08022 Barcelona, Spain
http://obrasocial.lacaixa.es/laCaixaFoundation/home_en.html

Speakers' hotel

Hotel Balmoral Barcelona
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B·DEBATE International Center for Scientific Debate BARCELONA

AN INITIATIVE OF: biocat "la Caixa" Foundation

B·Debate International Center for Scientific Debate Barcelona is a Biocat initiative with support from "la Caixa" Foundation. It drives first-rate international scientific debates, to foster dialogue, collaboration and open exchange of knowledge with prestigious national and international experts, to approach complex challenges of high social interest in life sciences. B·Debate sees debate as a powerful, effective way to generate knowledge and strives to help position Barcelona as a benchmark in generating knowledge and Catalonia as a country of scientific excellence.

More information: www.bdebate.org

CRAG CENTRE DE RECERCA EN AGRIGENÒMICA CSIC IRTA UAB UB

The **Center for Research in Agricultural Genomics** (CRAG) is a recently created research institute focused on the molecular mechanisms underlying plant and farm animal biology and to the applications of molecular approaches to the breeding of species that are important for food production. CRAG is a joint initiative of CSIC, the main public institution for research of the Spanish Government, IRTA, the institution for agricultural research of the Catalan Government, UAB, the Autonomouos University of Barcelona and UB, the University of Barcelona. Funding comes from the Catalan Government and the Consolider program awarded by the Spanish Government. The CRAG aims to be a center of excellence, based in Southern Europe but open to the surrounding regional areas, with an international strategy based on the attraction, maintenance and motivation of highly qualified and professional human resources.

More information: www.cragenomica.es

COLLABORATORS

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VIB (Flemish Institute for Biotechnology) is a life sciences research institute in Flanders, Belgium. With more than 1 300 scientists from over 60 countries, we perform basic research into the molecular foundations of life. VIB is an excellence-based entrepreneurial institute that focuses on translating basic scientific results into pharmaceutical, agricultural and industrial applications. VIB works in close partnership with four universities – UGent, KU Leuven, University of Antwerp and Vrije Universiteit Brussel and is funded by the Flemish government. VIB develops and disseminates a wide range of science-based information about all aspects of biotechnology.

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