

Simposio Internacional / *International Symposium:*

Siguiendo el camino de Alberto Sols: homenaje en el centenario de su nacimiento

In the footsteps of Alberto Sols: a homage on the centennial of his birth

Madrid, 20 y 21 de febrero de 2017 / *February 20-21, 2017*

ABSTRACTS

SESSION I: YEASTS AS EXPERIMENTAL MODELS

From yeast hexokinases to aminosugars metabolism. A long and winding road

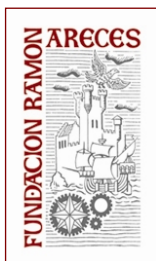
Carlos Gancedo

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Hexokinase was one of Sols's favourite enzymes and, indeed, it is a notable protein. In the yeast *Sacharomyces cerevisiae*, inhibition of hexokinase by trehalose-6-phosphate plays an important role in regulating glycolytic flux (1), and one of its isoenzymes, hexokinase 2, participates in the catabolite repression of several enzymes (2).

Sols' dictum that "enzymes are specific but only to some extent" affects also *S. cerevisiae* hexokinase, which can phosphorylate different sugars, some of which cannot be used as carbon sources by this yeast. This is the case of glucosamine which in this species acts as a non-metabolizable glucose analogue which hinders growth. As such, glucosamine has been used to obtain mutants insensitive to catabolite repression by selecting for growth on non-fermentable carbon sources in the presence of glucosamine.

We addressed the question of why *S. cerevisiae* does not use glucosamine as carbon source. Glucosamine utilization proceeds through the deamination and isomerization of glucosamine-6-phosphate to fructose-6-phosphate by glucosamine-6-phosphate deaminase but *S. cerevisiae* lacks the gene encoding this enzyme. Therefore the product of the phosphorylation of glucosamine by *S. cerevisiae* hexokinase cannot be further metabolized. In our previous studies on the N-acetylglucosamine (NAGA) utilization pathway in the non-conventional yeast *Yarrowia lipolytica* we identified the gene encoding that protein and by expressing it in *S. cerevisiae* we have generated a strain able to grow on glucosamine as carbon source. We have studied several physiological properties of this strain and will discuss our current results.



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Other studies on aminosugars metabolism have shown that one of the enzymes of the N-acetylglucosamine (NAGA) utilization pathway in *Y. lipolytica*, NAGA kinase, seems to be a moonlighting protein, a group of proteins that doubtless would have challenged Sols's ideas on enzyme specificity even taken into account his above mentioned dictum.

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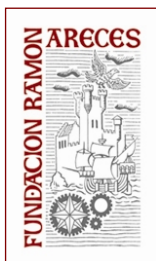
The role of the protein Trehalose 6-P synthase and its product T6P in the regulation of carbon and energy homeostasis in the yeast *Saccharomyces cerevisiae*

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The known function of trehalose-6-P synthase (Tps1) in the yeast *Saccharomyces cerevisiae* is to catalyse the first reaction leading to trehalose, a disaccharide that is considered to act as both a stress protectant and an energy reserve in yeast. However, besides its catalytic function, Tps1 may have additional functions in carbon and energy metabolism whose original precept goes back more than 40 years ago, with the isolation an odd mutant termed '*fdp1*' or '*cif1*' (1) that was characterized by its inability to grow on fermentable sugars, albeit exhibiting wild type activity of all glycolytic enzymes. In the year 90, the Gancedo' group showed that this mutant was defective in the gene encoding Tps1 (2). Two models have been proposed to account for the function of Tps1 in controlling glycolysis, namely (i) a restriction of the glucose influx due to inhibition of hexokinase by T6P, and (ii) the Pi-regeneration associated with trehalose cycling. However, several phenotypes of *tps1* null mutant including sporulation deficiency, hypersensitive to stress, respiratory chain malfunctioning, etc, could not be explained by neither of these two models, raising the question whether this role could be brought about by the protein itself independently to its catalytic function. We addressed this question by constructing catalytically inactive variants of Tps1. Meanwhile, we combined this strategy with the use of a yeast strain able to accumulate trehalose independently of the Tps1-dependent biosynthetic pathway to revisit the trehalose function in yeast.

In this presentation, I will first show that the Tps1 protein, and not trehalose, is indispensable to protect yeast from stress (3), including heat stress and cold-freezing shock. I will also show that Tps1 and not trehalose prevents cells from spontaneous apoptotic cell death and warrant a normal chronological lifespan (4). In both situations, we



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showed that the presence of Tps1 protein prevents the rapid drop of ATP that is occurring in response to stress and at the onset of apoptosis. Least but not last, I will propose a new model of how Tps1 and its product T6P regulates yeast glycolysis. As emphasized shortly above, yeast cells defective in Tps1 are unable to grow on glucose and this defect is merely due to an imbalance of glycolysis leading to a drop of ATP and a massive accumulation of sugars phosphates upon glucose addition. We found that this glycolytic imbalance is the consequence of a lack of interaction and concurrent inhibition of the *HXK2* encoding the major sugar kinase by Tps1. Moreover, this regulatory function of Tps1 protein is complemented by its product T6P which in a yet uncharacterized manner promotes the rapid switch from respiration to the fermentation of the yeast cell.

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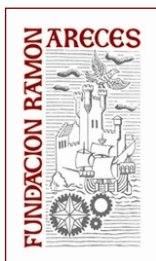
Pathway swapping: a new approach to simply and efficiently remodel essential native cellular functions

Pascale Daran-Lapujade, Niels G.A. Kuijpers, Daniel Solis-Escalante, Marijke A.H. Luttkik, Markus M.M. Bisschops, Francine Boonekamp, Marcel van den Broek, Jack T. Pronk and Jean-Marc Daran

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Spectacular developments in the field of synthetic biology have enabled the introduction of complete new pathways to living cells. However, the mosaic design of microbial genomes hinders the large-scale remodeling of their core machinery required to obtain a profound understanding of its governing regulatory principles and thereby to enhance the performance of industrial microbes. To overcome this limitation, we introduce the concept of 'pathway swapping'. Using as paradigm glycolysis, nearly-ubiquitous and essential metabolic highway for sugar utilization, we constructed a *Saccharomyces cerevisiae* platform enabling the quick and easy replacement of the 26-isoenzymes native glycolysis by simplified, heterologous synthetic versions. Yeasts carrying synthetic glycolyses from *Saccharomyces kudriavzevii* and mosaic glycolysis mixing yeast and human genes were successfully constructed and were able to grow in chemically defined minimal media. This work paves the way for a modular approach to engineering of central metabolism.

Keywords: Synthetic glycolysis, *Saccharomyces cerevisiae*, synthetic biology, modular pathway engineering.



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Lipid homeostasis: a hot topic in cold stress

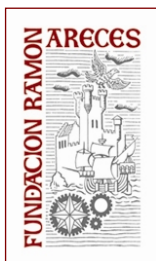
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Lipid composition of the plasma membrane is key for a number of essential cellular processes that depend on its functionality. Previous work by our group provided evidence suggesting that inositol pyrophosphates respond to changes in the content of PI(4,5)P₂ levels, leading to the regulation of the activity of the Pho80-Pho85 kinase complex and the yeast phosphatidate phosphatase Pah1, and the content of triacylglycerides and phospholipids. Recent results have also shown that PI(4,5)P₂ levels decrease during a downward shift in temperature. Interestingly, cold also induces an increase in the inositol pyrophosphate IP₇, as measured by a Pho85 reporter, decreases Pah1 activity and increases the expression of *INO1* and the synthesis of phospholipids. We also found that cold treatment elevates the content of Orm2, a negative regulator of the sphingolipid synthesis pathway, and the subcellular localization of the kinase Ypk1, a yeast orthologous of the mammalian SGK1-3 kinases, which is activated by Pkh1/2. The plasma membrane associated Pkh1/2 protein kinases contain a pleckstrin homology domain that enables them to bind PI(4,5)P₂. Altogether, these observations suggest a role of PI(4,5)P₂ in the perception and signaling of changes in ambient temperature that alters the content of inositol pyrophosphates and the activity of the Pkh-Ypk regulatory module, and leads to a dramatic change in the plasma membrane lipid composition and properties.



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SESSION II: ENZYMOLOGY AND METABOLIC REGULATION

Functional implications of enzyme structure: the case of mammalian phosphofructokinase

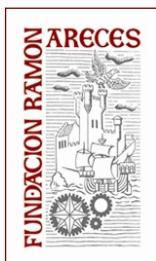
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The work of Alberto Sols was of crucial importance for the understanding of enzyme catalysis and regulation, and the physiological control of metabolism. His scientific work was also essential for the initiation in Spain of biochemical research with international relevance in the early sixties of the last century. Additionally, some of his achievements in basic research were seminal for further developments within the field of clinical medicine. In this talk, I will present some of our contributions to the significance of protein structure for enzyme function in the case of phosphofructokinase (PFK), a characteristic allosteric enzyme in which Alberto Sols was also interested.

PFK is a key regulatory enzyme of glycolysis, converting fructose 6-phosphate (Fru-6-P) into fructose 1,6-bisphosphate, whose activity is tightly controlled by various metabolites that bind at different allosteric sites. Among other regulatory mechanisms, most eukaryotic PFKs are highly activated by fructose 2,6-bisphosphate (Fru-2,6-P₂) and inhibited by MgATP. Three types of subunit isozymes exist in mammals, C, M, and L, which form homo- and heterotetramers. In eukaryotes, PFK has homologous N- and C-terminal domains thought to result from duplication, fusion and divergence of a primitive prokaryotic gene. Sequence manipulation studies indicated that the catalytic site is contained in the N-terminal half, whereas the Fru-2,6-P₂ allosteric site is contributed by the C-terminal half; the two sites being shared across the interface between subunits aligned in an antiparallel orientation to form each mammalian dimer. This model was consistent with our report of the electron microscopy (EM) structure of human muscle PFK-M and the crystal structure of the enzymes from yeasts and that of PFK-C. We have also shown that the catalytic N-terminus is in fact capable of forming a functional PFK active site, and that the C-terminus, although not catalytic, is needed for stability of the enzyme, in addition to accommodate extra regulatory sites.

The EM analysis of human PFK-M in the presence of Fru-6-P disclosed an unusual 3-dimensional structure for the tetramer, showing the presence of a prominent channel in one of the dimers but not in the opposite one, revealing that they are in greatly different conformations -open and closed, respectively. Fitting of the bacterial structures into the EM model suggested disruption of the Fru-6-P catalytic and the Fru-2,6-P₂ allosteric sites in the cavity-containing dimer, precluding the coordinated binding of ligands. Thus, only the dimer in the closed conformation may have normal-acting binding sites. To evaluate whether all these sites are functionally equivalent or not, we have generated hybrid



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enzymes with different proportions of wild-type subunits and mutant subunits, which were altered in either the catalytic site for Fru-6-P or the allosteric site for Fru-2,6-P₂. Kinetic and regulatory analyses with the isolated hybrid enzymes showed that the four binding sites per tetramer, for either Fru-6-P or Fru-2,6-P₂, are indeed functional although they do not act simultaneously, but with an alternation from one dimer to the other. The resulting model for PFK functioning implies that Fru-6-P/Fru-2,6-P₂ binding induces the closed dimer conformation, which turns into the open conformation as either the reaction products or the allosteric effector are released.

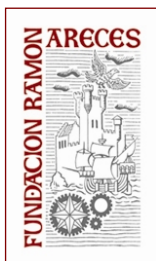
Metabolite control of hepatic gene expression by old and new anti-hyperglycaemic drugs

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Small molecule activators of glucockinase (GKAs) have been extensively explored as potential anti-hyperglycaemic drugs for type 2 diabetes (T2D). The GKAs were remarkably effective at lowering blood glucose during early therapy but then lost their efficacy after 4 weeks during clinical trials. A crucial question is why do drugs used for metabolic disease lose their efficacy chronically? Is this a complex mechanism of insulin resistance and steatosis or can it be simulated in a cell model? We used primary hepatocytes to test the hypothesis that GKAs raise hepatocyte glucose 6-phosphate, (G6P, the glucokinase product) and down-stream metabolites with consequent repression of the liver glucokinase gene (*Gck*). We then explored how metformin (dimethyl biguanide) the oldest and most widely prescribed drug globally for metabolic disease affects hepatocyte metabolites and control of gene expression.

Challenge of hepatocytes with high glucose raised cell G6P concomitantly with *Gck* repression and induction of *G6pc* (glucose 6-phosphatase) and *Pk1r* (pyruvate kinase). A GKA mimicked high glucose by raising G6P and fructose-2,6-bisphosphate, a regulatory metabolite, causing a left-shift in glucose responsiveness on gene regulation. Fructose like the GKA repressed *Gck* but modestly induced *G6pc*. 2-Deoxyglucose, which is phosphorylated by glucokinase, but not further metabolised caused *Gck* repression but not *G6pc* induction, implicating the glucokinase product in causing *Gck* repression. Metformin



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counteracted the effect of high glucose on the elevated G6P and fructose 2,6-bisphosphate and on *Gck* repression, recruitment of Mlx-ChREBP to the *G6pc* and *Pklr* promoters and induction of these genes showing converse effects from the GKA. We next studied the mechanism by which metformin lowers G6P in liver cells challenged with high substrate to simulate metabolic disease.

Conclusions: 1. Elevation in hepatocyte G6P and downstream metabolites with consequent liver *Gck* repression is a candidate mechanism for the loss of GKA efficacy during chronic therapy. 2. Cell metformin loads within the therapeutic range reverse the effect of compromised metabolite homeostasis with consequent effects on liver gene regulation.

Unveiling the metabolic plasticity underlying metastatic potential: a systems medicine approach to identify new drug targets

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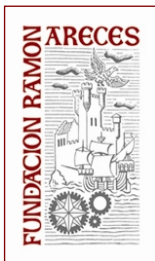
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Progression towards metastasis is initiated by a cellular process known as epithelial-mesenchymal transition (EMT) and followed by the participation of a minority of malignant cells known as tumor-initiating cells (TICs). Using a well characterized clonal prostate neoplastic cell subpopulations displaying stable and distinct EMT (epithelial-mesenchymal transition) or e-CSCs (metastatic epithelial stem cell) phenotypes, and combining metabolomics, ¹³C-fluxomics and genome scale metabolic network reconstruction approaches, we have characterized differential key



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features in their metabolic reprogramming with potential clinical implications. Moreover, analysis of transcriptomic data yielded a metabolic gene signature for our e-CSCs, consistent with the metabolomics and fluxomics analysis that correlated with tumor progression and metastasis in prostate cancer and in 11 additional cancer types, suggesting potential biomarkers and therapeutic targets to effectively forestall metastasis.

Finally, workflow for ¹³C-fluxomics (in development in the framework of the e-infrastructured project PhenoMeNal www.phenomenal-h2020.eu/home/) to facilitate the use of existing ¹³C-fluxomics tools and metabolomics data repositories as MetaboLights (www.ebi.ac.uk/metabolights) is also presented.

(Part of these results have been published in Stem Cells 2016;34:1163-1176)

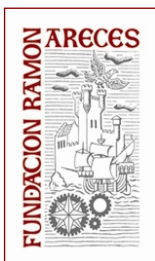
- Spanish Government -MNIC-EuropeanComissionFeder-Una manera de hacer Europa-SAF2014-56059-R
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- European Comission (H2020-EU.1.4.1.3.- development, deployment and operation of ICT-based e-infrastructures, grant 654241).- PhenoMeNal: A comprehensive and standardised e-infrastructure for analyzing medical metabolic phenotype data.
- Marta Cascante acknowledges the support received through the prize "ICREA Academia" for excellence in research, funded by ICREA foundation – Generalitat de Catalunya

Striking a balance between cellular growth and homeostasis

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Altered tumor cell metabolism is now firmly established as a hallmark of human cancer. Downstream of oncogenic events, metabolism is re-wired to support cellular energetics and supply the building blocks for biomass. Rapid, uncontrolled proliferation results in tumor growth beyond the reach of existing vasculature and triggers cellular adaptations to overcome limiting nutrient and oxygen delivery. However, oncogenic activation and metabolic re-programming also elicit cell intrinsic stresses, independent of the tumor



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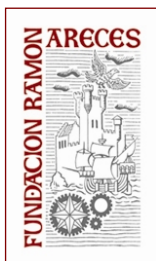
microenvironment. To ensure metabolic robustness and stress resistance, pro-growth signals downstream of oncogene activation or tumor suppressor loss simultaneously activate homeostatic processes. Here, I will summarize recent studies describing adaptive mechanisms co-opted by common oncogenes and tumor suppressor, including *Vhl*, *mTOR*, *MYC*, and *RAS*. Recurrent themes include: (1) coordination of oncogene-induced changes in protein and lipid metabolism to sustain endoplasmic reticulum homeostasis, (2) maintenance of mitochondrial functional capacity to support anabolic metabolism, (3) adaptations to sustain intracellular metabolite concentrations required for growth, and (4) prevention of oxidative stress. Ultimately, an understanding of the adaptations required downstream of specific oncogenes could reveal targetable metabolic vulnerabilities.

SESSION III: MOLECULAR PATHOLOGY

Revisiting macrophage metabolism: Reprogramming macrophage function and its use in medical diagnosis

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Recent advances in the knowledge of macrophage ontology, self-renewal and infiltration in different tissues have shown a previously unexpected plasticity. These properties offer new alternatives for the manipulation of macrophages in diagnosis and therapeutics of prevalent diseases, such as atherogenesis, oncology, infection or inflammation. At the same time, interference of their metabolic programs may influence their function and viability leading to a reprogramming of their fate in the course of inflammatory pathologies. Mammalian macrophages are present in a large variety of locations, playing distinct functions that are determined by its origin and by the nature of the activators present in the environment. Current view on macrophage activation has allowed a classification as pro-inflammatory (M1 polarization) or anti-inflammatory, pro-resolution (resetting the inflammatory response) and deactivation (M2 polarization), these profiles coexisting in the course of the immune response, and playing a relevant functional role in the onset of inflammation. Several groups analyzed the metabolic aspects associated with macrophage activation trying to answer the question about what changes in the regulation of energy metabolism and biosynthetic precursors (NADPH, riboses, etc.) accompany the different types of polarization and to what extent these physiological inputs are necessary for a given activation phenotype. The interest of these studies is to envisage the possibility to regulate macrophage function by altering their metabolic activity as a complementary strategy to regulate their participation in the orchestration of inflammatory responses, recruitment of other myeloid and lymphoid lineages. Our data show that regardless of the



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challenges used to activate the macrophage, and the availability of energy substrates, these cells are in more than 90% glycolytic, with limited use of other fuels for energy purposes; however, the pathways to generate metabolites from the TCA and glutaminolysis are fully functional and used for other purposes, in particular lipogenesis, membrane remodelling and release of bioactive lipid mediators that impact on neighboring cells. In this context, we have investigated the role of macrophages in the development of atherogenesis, its diagnosis using molecular imaging approaches and its contribution to plaque stability and culprit and non-culprit acute coronary events. These studies allowed us to develop new strategies to evaluate functional atheromas with different radiotracers, and to stabilize the atherogenic lesions using specific metabolic-based signatures of the activated macrophage.

A metabolite repair enzyme destroys two toxic glycolytic side products in mammalian cells

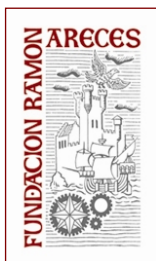
Emile van Schaftingen, Francesca Baldin, Guido Bommer

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It is commonly assumed that enzymes of metabolic pathways operate with near-perfect specificity and efficiency. In contrast to this, recent work from us and others has revealed that many metabolic enzymes show weak side-activities towards substrates that resemble their physiological substrates. In some cases, the resulting side-products can accumulate and have dramatic metabolic effects unless they are eliminated by dedicated enzymes, called metabolite repair enzymes. As an example of this, the non-classical metabolite L-2-hydroxyglutarate is formed by a side-reaction of mitochondrial L-malate dehydrogenase (MDH2). This metabolite is normally eliminated by a specific enzyme, L-2-hydroxyglutarate dehydrogenase (FAD). However, if this enzyme is inactivated by mutations, the small side-reaction of MDH2 suffices to cause the accumulation of millimolar concentrations of L-2-hydroxyglutarate in tissues, leading to a progressive leukoencephalopathy and an increased incidence of brain tumors in humans.

In our quest to identify new metabolite repair enzymes, we are particularly interested by enzyme side activities that produce compounds with a predicted toxicity, because the cells must have a mechanism to prevent the accumulation of such toxic molecules. We hypothesized that this would be the case for a side activity of glyceraldehyde-3-phosphate dehydrogenase resulting in the conversion of erythrose-4-P to 4-P-erythronate, a very potent inhibitor ($K_i < 1 \mu\text{M}$) of 6-P-gluconate dehydrogenase. We decided therefore to search for a phosphatase that would destroy 4-P-erythronate.

We found indeed that mammalian tissues contain a phosphatase acting very well on 4-P-erythronate. We purified this enzyme and identified it as a phosphatase known to act on 2-P-glycolate and therefore named PGP (phosphoglycolate phosphatase). Analysis of the specificity of this enzyme indicated that it acts best on 4-P-erythronate, 2-P-glycolate



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and 2-P-L-lactate, and that it barely acts, if at all, on classical phosphate esters belonging to glycolysis or the pentose-phosphate pathway.

As expected, inactivation of the PGP gene in HTC116 cells with the CrispR/Cas9 technique led to marked (>10-fold) increases in the concentrations of 4-P-erythronate and 6-P-gluconate. It did not lead to detectable accumulation of 2-P-glycolate, but to a dramatic increase in the concentration 2-P-L-lactate, a phosphate ester whose presence had never been reported before in living cells. We obtained evidence for the formation of 2-P-L-lactate by a side activity of pyruvate kinase, which slowly phosphorylates L-lactate in an ATP-dependent reaction. Among the other metabolic changes that we noticed were an $\approx 50\%$ decrease in the glycolytic flux and an $\approx 80\%$ decrease in the concentration of the glycolytic activator fructose 2,6-bisphosphate, which is presumably due to inhibition of 6-phosphofructo-2-kinase by 2-P-L-lactate.

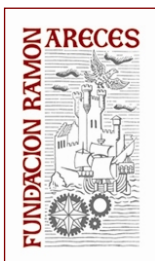
These findings led us to the conclusion that PGP serves in mammalian cells to eliminate two glycolytic side products that are formed by two major enzymes of glycolysis and that its presence is required for the correct operation of glycolysis and the pentose phosphate pathway. Other data showed that the homologous enzyme in yeast, Pho13, plays a similar metabolite repair role by dephosphorylating 4-P-erythronate and 2-P-glycolate.

Reactive oxygen species-friend or foe in gut health

Ulla G Knaus

University College Dublin. Ireland.

Maintaining the redox balance between generation and elimination of reactive oxygen species (ROS) is critical for health. Continuously elevated ROS levels will result in oxidative damage and development of disease, but likewise insufficient ROS production will be detrimental to health. Reduced or even complete loss of ROS generation originates mainly from inactivating variants in genes encoding for NADPH oxidase complexes (NOX, DUOX). Deficiency in phagocyte NOX2 function due to loss-of-function variants (mainly *CYBB*, *NCF1*) causes chronic granulomatous disease (CGD), an inherited immune disorder characterized by severe infections, which is often accompanied by colitis resembling Crohn's disease. Reduced ROS generation by partially inactivating variants in subunits of the NOX2 complex or in *NOX1* or *DUOX2* expressed in the colon epithelium constitutes a risk factor for developing very early onset inflammatory bowel disease



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(VEOIBD), thereby strengthening the notion that sufficient ROS generation is essential for intestinal homeostasis. While the role of high ROS concentrations for microbial killing by phagocytes is evident, the importance of releasing low H_2O_2 concentrations via mucosal NOX1 or DUOX2 as microbiota modifier or host defense mechanism remains unclear. I will present our current knowledge in colitis-associated ROS deficiency in patients, combined with recent insights of how nano to submicromolar H_2O_2 in the intestine alters the microbiota composition and downregulates bacterial virulence factors. Examples will be the regulation of the LEE pathogenicity island in enteropathogenic *E. coli* and the tyrosine phosphorylation network in several pathogens. These H_2O_2 -mediated processes culminate in a host-initiated antivirulence strategy that reduces the fitness of pathogens in the extracellular space.

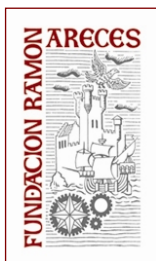
Treating diabetes with an insulin and glucokinase gene therapy

Fátima Bosch

Centro de Biotecnología Animal y Terapia Génica and Departamento de Bioquímica y Biología Molecular. Universidad Autónoma de Barcelona.

Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM). Bellaterra. Spain.

Diabetes is associated with severe secondary complications, caused largely by poor glycemic control. Treatment with exogenous insulin fails to prevent these complications completely, leading to significant morbidity and mortality. Achievement of normoglycemia with exogenous insulin treatment requires the use of high doses of hormone, which increases the risk of life-threatening hypoglycemic episodes. We previously demonstrated that it is possible to generate a “glucose sensor” in skeletal muscle through co-expression of glucokinase (Gck) and insulin (Ins), increasing glucose uptake and correcting hyperglycemia in diabetic mice. We have also demonstrated long-term efficacy of this approach in a large animal model of diabetes. A one-time intramuscular administration of adeno-associated viral vectors of serotype 1 (AAV1) encoding for Gck (AAV1-Gck) and Ins (AAV1-Ins) in diabetic dogs resulted in normalization of fasting glycemia, accelerated disposal of glucose after oral challenge, and no episodes of hypoglycemia during exercise for long-term (~8 years) after gene transfer. This was associated with recovery of body weight, reduced glycosylated plasma proteins levels, and long-term survival without secondary complications. The persistence of vector genomes and therapeutic transgene expression years after vector delivery was documented in multiple samples from treated muscles, which showed normal morphology. Thus, our studies demonstrate the long-term



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efficacy and safety of insulin and glucokinase gene transfer in large animals and, specially, the ability of the system to respond to the changes in metabolic needs as animals grow older. These safety and efficacy results will be key data for supporting a first-in-human study for patients with diabetes. Nevertheless, for clinical translation, the approach requires further development. In this regard, the generation of single AAV vectors that encode both genes is underway. Considerations that further support the applicability of the Gck and Ins gene therapy for the treatment of diabetes will also be discussed.

Supported by grants from Ministerio de Economía y Competitividad, Plan Nacional I+D+I (SAF2011-24698 and SAF2014-54866-R), Generalitat de Catalunya (2014SGR-1669 and ICREA Academia Award).

SESSION IV: NEW GENERATIONS, NEW PERSPECTIVES

Oxygen as a developmental cue in plants

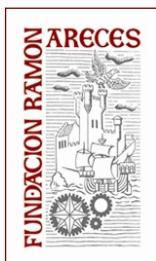
Miguel A. Blázquez

Instituto de Biología Molecular y Celular de Plantas. CSIC-UPV. Valencia. Spain.

The pervasive role of light as a modulator of plant development has often hidden the fact that additional environmental signals can trigger specific differentiation programs. Among those, oxygen availability has long been known to affect metabolic processes, and hypoxia is usually considered as a stress factor that impairs growth. However, we have found evidence for a beneficial role of hypoxia during the early stages of seedling development right after seed germination. More specifically, the formation of the apical hook that protects the stem cell niche from erosion when the seedling finds its way towards the soil surface requires the low oxygen levels normally found underground.

The molecular mechanism that allows the perception of oxygen levels depends on the degradation of Group-VII ERF transcription factors (ERFVII) through the N-End Rule Pathway, whose first step is the oxydation of the N-terminal Cys residue. At low oxygen levels, ERFVII become stable and promote apical hook formation, while increasing oxygen levels as the seedling approaches the surface promote ERFVII tagging for degradation and apical hook unfolding.

We propose that, in addition to light and temperature, seedlings monitor the gaseous environment to establish the optimal differentiation program.



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Single-molecule Biophysics: understanding protein machines one at a time

Fernando Moreno-Herrero

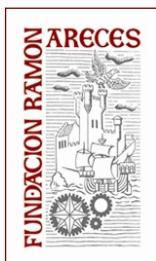
Centro Nacional de Biotecnología (CNB). CSIC. Madrid. Spain.

Today, we know that many enzymes and proteins involved in the proper functioning and maintenance of the cell appear in a low-copy number. At this scale level, each molecule counts and proper understanding of a biological process requires monitoring the activity of these individual proteins in action. Moreover, multiple biological processes are time resolved and fundamentally mechanical, following a sequence of events exquisitely coordinated by force, and proving again that life is an out of equilibrium process.

Traditional biochemical methods lack this single-molecule approach because they provide information on the ensemble, disregarding individual, out-of-the-mean, behaviors that as mentioned above may be relevant for the proper functioning of the cell.

Manipulation and visualization of single molecules is now possible by means of a myriad of biophysical techniques that can capture the presence and activity of single protein machines involved, for instance, in replication, transcription, DNA maintenance and repair, etc. These DNA transactions are essential for the cell, thus it is not surprising that these topics have attracted much attention of researchers over the last years.

Here, I will introduce Magnetic Tweezers as a biophysical technique that allow us to investigate protein machines involved in DNA processing one at a time. Magnetic Tweezers is based on an inverted optical microscope and provides a measurement of the extension of a single DNA molecule over time at a given force, while proteins are acting on the DNA. I will show recent works of helicases and other proteins involved in DNA repair and chromosome maintenance. Common to all these works is that protein activity is indirectly inferred by changes in the extension of a tethered DNA molecule. This precludes direct identification of the protein acting on the DNA. Prompted by this limitation, we have recently combined Magnetic Tweezers with fluorescence. This state of the art technology opens new possibilities allowing us to correlate biological activity with the identity of DNA-bound protein complexes and to determine their binding position along DNA.



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SESSION V: SOLS AND SOCIETY

Our work in Sols's lab at the CIB

Margarita Salas

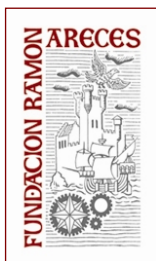
Centro de Biología Molecular "Severo Ochoa". CSIC-UAM. Madrid. Spain.

I started to work in Alberto Sols' laboratory in January 1961 thanks to a letter written by Severo Ochoa in which he asked Sols to take me to carry out a Ph.D. Thesis. Sols accepted me right away since he could not refuse to something that Ochoa asked him. Three months later, Eladio Viñuela also joined Sols' lab. My Ph.D. Thesis work dealt with the yeast glucose phosphate isomerase, the enzyme that converts glucose-6-phosphate into fructose-6-phosphate. We found that for this conversion, the open form of glucose-6-phosphate was produced, thus, the anomerization property of glucose phosphate isomerase. Eladio's Ph.D. Thesis work dealt with the yeast phosphofructo kinase and he found the allosteric properties of this enzyme.

In the meantime, Sols asked Eladio to try to find an enzyme in rat liver, different to the hexokinase (the enzyme that converts glucose into glucose-6-phosphate), that should have a high K_m for glucose. Eladio worked very hard and he succeeded to find such an enzyme that they called glucokinase. Very generously, Eladio asked me to join him in this work and we found that glucokinase disappeared in fasted and diabetic rats, and reappeared by feeding and glucose administration, respectively.

At that time, enzyme purification was carried out by ammonium sulphate and acetone or ethanol precipitation. I remember that we introduced column chromatography as a new tool for enzyme purification and, since there was no money to buy a fraction collector, we had to collect the fractions by hand, one by one.

Altogether, I must say that we were very lucky to be able to carry our Ph.D. Thesis work in Alberto Sols' laboratory. He was an excellent biochemist and we learned the enzymology



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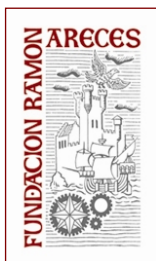
and basic biochemistry thanks to his teaching. I will always remember him with great gratitude as one of my teachers.

Alberto Sols, the hero I heard about

Félix Goñi

Departamento de Bioquímica. Universidad del País Vasco. Bilbao. Spain.

I have been invited to this symposium as President of the Spanish Biochemical Society, SEBBM from its Spanish official name. Everybody knows the truly unique role of Sols in the birth and development of our Society, of which he was the first President (1964-1968) but, to be honest, those were times of which I have heard, or about which I have read in books that are easily available and well known, not (despite my white hair) times that I have lived. Thus in the dilemma of saying some polite and accurate, though hardly felt, historical data, or re-living my own, even if indirect, remembrances of Sols, I have opted for the less intellectual and warmer attitude of the personal memoirs. In fact, apart from some formal introduction, I never exchanged a word with Sols, I was too young, and perhaps too provincial as well. However I heard a lot, and in the most enthusiastical terms, about him from my teacher and life-long mentor José María Macarulla (1932-2012). He was not a disciple of Sols, but he was his fervent admirer and old friend. Macarulla was teaching the 1st year Biochemistry course when I was an undergraduate, at Navarra Medical School, and I still remember when, lecturing on anaerobic glycolysis, he mentioned the contributions of Alberto Sols who, in Macarulla's words "could get the Nobel Prize, if they ever gave it again to a Spaniard". Such was his admiration for Sols, and such was his prophecy, unfortunately still unfulfilled. In later years, Macarulla would speak with fervour of Sols's publications, enjoying particularly those devoted to broad biochemical problems, that he would publish in (unthinkably today) non-indexed journals. I remember vividly "The myth of the charged coenzymes" against the clinical use of ATP *per os* or parenterally administered, or the one describing the "truly essential" aminoacids, i.e. those that our body synthesizes because we cannot dispense with them if they are not present in the diet. Of the scientific contributions of the mature Sols, Macarulla enjoyed his idea of assaying enzymes *in situ*, keeping the cell as intact as posible, and permeabilizing the plasma membrane to allow access to substrates and removal of end-products. I will close these brief remembrances with a reflection, considering the present situation and values of Molecular Biology in our world. When we read Sols's papers, the feeling of the work well made is immediately perceived, and the reasoning behind them is as fresh and enticing as it was forty years ago. Most of them remain absolutely valid to this day. And yet, let us look at the journals in which his great contributions were published. No Nature, no Science among them. Would have he, with the present day criteria, been able to apply with a minimum of success for a MINECO grant? Or for an RO1, for that matter.



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The internationalization of Spanish Biochemistry

Joan Guinovart

Universidad de Barcelona and Instituto de Investigación Biomédica (IRB Barcelona). Spain. President, International Union of Biochemistry and Molecular Biology (IUBMB).

The set-up of the International Union of Biochemistry (IUB, later IUBMB) in 1955 triggered the founding of the Spanish National Committee of Biochemistry in the same year -a requirement to apply for IUB membership. Sols was its first secretary, becoming its president in 1968. Spain was immediately admitted to IUB. The launch of the Spanish Society for Biochemistry (SEB, later SEBBM) did not come about until 1963 and was the result of the formation of the Federation of European Biochemical Societies (FEBS). Again, Sols played a key role in both processes. This period marked a crucial turning point regarding the integration of Spain in the international scientific landscape, which led to the organisation of the VI FEBS Congress in Madrid in 1969 under a difficult political context. Severo Ochoa made a significant contribution to promoting these activities. Around that time, Spain joined EMBO, but its involvement in EMBL had to wait until 1987.

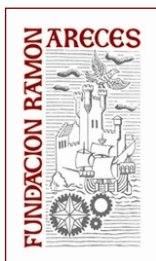
SEBBM is also an adherent society of PABMB (Pan-American Association for Biochemistry and Molecular Biology), where it plays an active role, promoting the participation of Spanish scientists at its meetings.

Relations with Portugal have a long tradition, reflected by the Luso-Spanish congresses that were promoted by Sols and N. van Uden and held for many years. Portugal actively participated in the IUBMB–FEBS Congress held in Seville in 2012, and Spain will be involved in the Congress to be held in Lisbon in 2021.

At the turn of the 20th century, SEBBM relations with Latin American societies were boosted by bilateral agreements, particularly with Chile and Argentina through the inclusion of the Severo Ochoa and Alberto Sols Lectures at the meetings of the societies of these countries (SChBBM and SAIB, respectively), while the Hermann Niemeyer and Luis F. Leloir Lectures are included in SEBBM Congresses. Similarly, SEBBM holds a joint biennial symposium with the Mexican Society, held alternately in each country.

Several occasional joint meetings have been organised with the French Society, and in 2017 Barcelona will host a FEBS 3+ Meeting, involving the participation of France and Portugal.

Nowadays, Spanish scientists representing SEBBM serve on the committees of all international biochemistry and molecular biology organisations, thus reflecting the recognition of Spanish science worldwide. The seed once planted by Sols and his contemporaries has flowered to give abundant fruit.



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Alberto Sols: his influence on the Medical School of the UAM

Juan Antonio Vargas

Dean, Facultad de Medicina. UAM. Madrid. Spain.

Professor Alberto Sols died on 10th August 1989, and three months later, on 15th November of the same year, an In Memoriam ceremony was organized by the Faculty of Medicine's Biochemistry Department, the Institute of Biomedical Research and the Centre for Biological Research, and held in the Autonomous University of Madrid's Faculty of Medicine. Today we are once again holding an essential event in honour and permanent memory of Professor Sols on the centenary of his birth in February 1917.

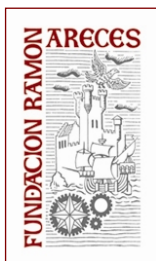
In the ceremony held in 1989, Severo Ochoa stated that Alberto Sols "had made a remarkable contribution to the recognition of Spanish science, giving rise to an unexpected science, biochemistry, and he was an authentic pioneer in our country". In addition, he highlighted his exceptional scientific endeavours together with his remarkable work teaching researchers, as well as his human facet being a good, honest, sympathetic and affectionate man.

His relationship with the Autonomous University of Madrid and the Faculty of Medicine began in 1972, when the decision was taken to transfer the Enzymology and Molecular Pathology Institute to the Campus of Medicine, thereby initiating a succession of scientific successes for the Biochemistry Department as well as the Faculty, united in a permanent effort to continuously improve the level of our teaching and research.

Professor Alberto Sols was a member of our faculty's first Board of Directors and his colleagues, such as Professor Reinoso, have never forgotten the amiable but deep discussions that took place during the early years, where concurring or differing opinions were the way to reach well-considered conclusions.

In the words of Professor Alberto Sols in a book commemorating the 20th anniversary of the Faculty of Medicine published during the year of his death, "We are proud of our origins and believe we have contributed to making our faculty the most prominent in our country". He continued, "The Biochemistry Department is prepared to enthusiastically commit itself to the future, devoting all its efforts so that our faculty reaches the most distinguished position possible in the panorama of national and international universities and science."

Unquestionably, and in agreement with Roberto Marco, the influence of Alberto Sols is profound and, without him, neither the Biomedical Research Institute, nor the Biochemistry Department of the Faculty of Medicine, nor the Autonomous University of Madrid would have existed in the form that we know today. On behalf of the Faculty of Medicine, we thank you Professor Sols for your scientific and humane legacy with gratitude from all the organizers of this ceremony.



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Closing lecture: Alberto Sols, the future is invented

Federico Mayor Zaragoza

Chairman of the Scientific Council.

Fundación Ramón Areces. Spain.

Alberto Sols had his way, to discover, to imagine. From his watch-tower he scouted activators, inhibitors, and other inter-and intra-cellular mechanisms of communication. "Research, said Professor Krebs, is to see what everybody can see and to think what nobody has thought". Alberto Sols was always in the forefront of a new thinking. Sugars and enzymes occupied his scientific activity.

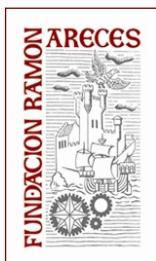
I first met him in February 1957, when he taught a first special course on Enzymology. After a long period of biological chemistry in Spain, dynamic molecular biology entered with him. Among all his "local" collaborators in the early steps Carlos Asensio, Claudio Fernández de Heredia, Carlos Gancedo, Roberto Marco..., I would like today to mention specially Gertrudis de la Fuente, who passed away very recently. I had always a great admiration and esteem for her.

At that time Sols had already done a long run. Born in Sax, Alicante, in 1917, he knew very well the proverb of the sailors: "There is never good wind for those who don't know where to go". And he acted accordingly. In 1947 the Spanish Superior Council of Research sponsored his first trip to Oxford, to participate in an important Congress of Physiology. In October 1950 he wrote to Professor Carl Cori, who three years before, together with his wife Gerty and the Argentinean Bernardo Houssay had been awarded the Nobel Prize of Physiology. I will never forget the sentence I read in the Laboratory of Houssay when I visited it in 1965 with his "successor" Luis Federico Leloir: "There is no applied science if there is no science to apply".

On September 1951, Sols started to work with Carl and Gerty Cori in the United States and after two and a half years, in January 1954, he travelled from New York to Algeciras, back to Spain. He carried with him reagents bought with his own money and a Klett colorimeter, the tools to start his research.

In Spain his relationship with Angel Santos Ruiz, was important and very fluent, particularly through their students devoted to research. Santos Ruiz had introduced the studies of biochemistry in 1939 in the Faculties of Pharmacy, and was the President of the Spanish Committee of the International Union of Biochemistry (IUB).

In 1961, I had the unforgettable occasion of travelling with Sols and Professors Santos Ruiz and F. Ponz to participate in the World Congress of Biochemistry held in Moscow. In that same year, I worked with him in the drafting of the Spanish Society of Biochemistry Statutes and I was very honoured to attend at his side, in London, in 1964, the founding session of the Federation of the European Biochemical Society (FEBS) to which the fledgling Spanish Society of Biochemistry (SEB) adhered.



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I vividly remember the SEB meeting in Granada in 1967, with Carl Cori, Severo Ochoa, Hugo Theorell, and two years later, in 1969, the very important FEBS meeting in Madrid, with Carl Cori, Feodor Lynen, Hans Krebs, Hugo Theorell among others. Sols was the driving force behind the organization of this meeting to which he devoted an immense amount of thinking, work and energy. Severo Ochoa, Nobel Prize in 1959, was also a critical person for the success of that meeting. He and Sols became the wider wings for the promotion of biomedicine in Spain, particularly in the Campus of the Autonomous University of Madrid. Two Research Institutes bear today their names as a token of gratitude for their efforts and their scientific values.

Sols was in charge, from the very beginning, of the Department of Biochemistry of the newly created Faculty of Medicine of the Autonomous University in 1969 and some years later he was appointed - when I was Under Secretary of Education and Science- full Professor of the Spanish University, taking into account his outstanding biography.

Alberto Sols had knowledge, imagination, perseverance; he was tirelessly sowing seeds in order to better discover and invent. The “new biochemists” have a lot to learn taking into account the “roots” of the present developments.

A remembrance of Sols will be perhaps incomplete without a mention to Angelines, his wife, who always supported him in his labour.

The degree of excellence reached by Alberto Sols remains a reference for all of us.

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