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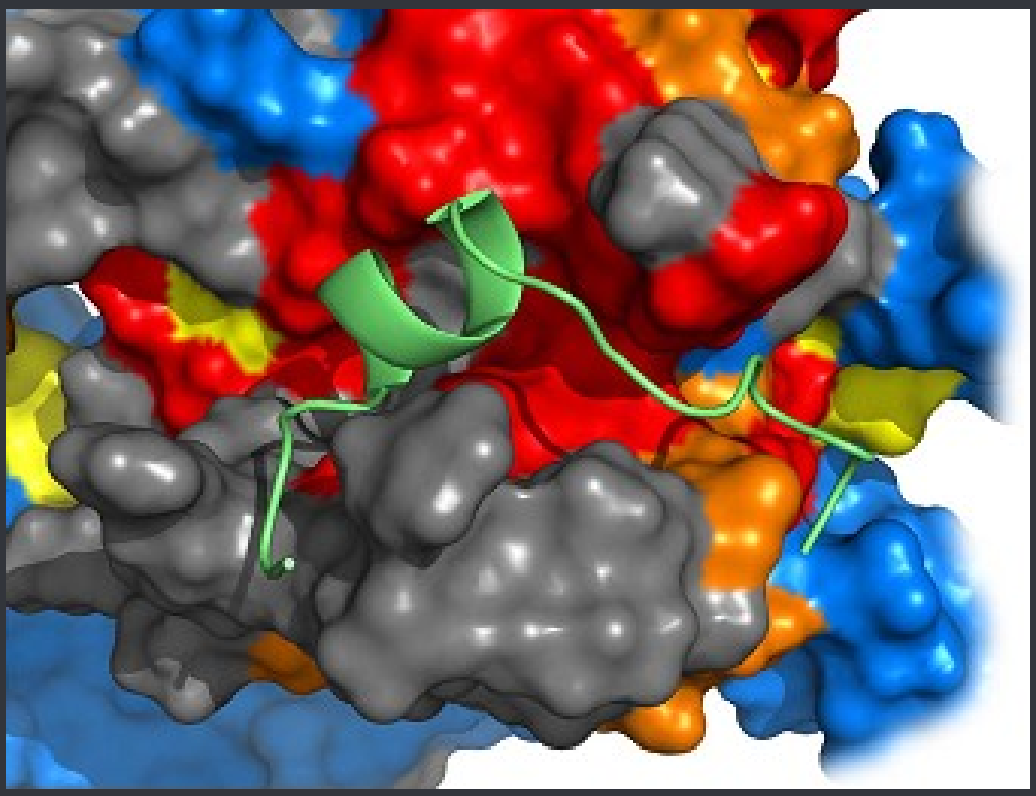

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In this issue

Biofísica Magazine

EDITORIAL / ANALYSIS

European Science after Brexit: Science as a cohesive political tool

Miguel A. De la Rosa, *Former FEBS Chairman. cicCartuja, Sevilla (Spain)*.

The result of the *Brexit* referendum – announced on the 23rd of June 2016 – was an unpleasant surprise for many inside and outside the UK. Shortly after the result was declared, an editorial was released by the journal Nature [1] stating that "Scientists – just like everybody else – have little idea what will happen now that the United Kingdom has voted to exit the European Union". Much has been discussed since then, but in reality little has advanced, and almost one year on, we still have no idea. Indeed, up until the 29th of March 2017 Theresa May's government had not officially communicated with the European Union about Brexit, almost coinciding – as fate would have it – with celebrations commemorating the 60th anniversary of the 1957 founding *Treaty of Rome*.

The impact of Brexit on a EU without the UK is unpredictable, and few people are willing to take the risk of anticipating possible political, social and, in particular, scientific consequences. What is clear, however, is a widespread fear about a tough economic adjustment for both, the EU and the UK. Regarding the impact of Brexit on the Spanish economy, the newspaper El País recently ran an article (March 11th, 2017 [2]) referencing an official document prepared by the Permanent Representation of Spain to the EU Commission on Brexit, which is headed by the vice-president of the government, stating that "The Spanish economy will lose between 2 – 4 points in growth, exports will fall by about 500 million annually and British abandonment will force Spain to contribute 888 million more to Europe". Predictions indicate that tourism – a key sector for the Spanish economy – will be most affected, particularly in the regions of Andalucía, Baleares, Canarias and Valencia.

The science and technology sector, in comparison, does not appear to be seriously affected in Spain, due to its small weighting in the overall economy and industrial fabric of the country. However, it could be damaged at a British and European level on two fronts: Firstly, for the significant contribution that the UK makes to the European budget. And secondly, for the British scientific leadership and frequent participation in European programmes, either as a host country for scientists (especially the young) or as a partner in scientific networks and integrated projects, along with the strong capacity to influence

decision-making in Brussels and to define future political strategies.

The *alarms* concerning the possible implications of Brexit started to sound before the result of the referendum was known, particularly among scientists working in the UK. In the same editorial of Nature cited above [1] it was pointed out that "Researchers are already mobilizing to lobby for the United Kingdom to remain a participant in EU science programmes (...) But it's unclear whether the United Kingdom will still be attractive to talented researchers". These fears are well founded. If the UK imposes restrictions on the free movement of people in the wake of Brexit, it is probable that Britain will appear less attractive to the European scientific community and, in turn, the EU may limit the participation of the UK in its research and innovation programmes. A similar scenario happened in 2014, when the access of Swiss researchers to the H2020 programme was restricted after the positive national vote to reduce immigration.

If the UK imposes restrictions on the free movement of people, it is probable that Britain will appear less attractive to the European scientific community. In turn the EU may limit the participation of the UK in its research and innovation programmes

The *Schengen agreement*, which allows the free movement of people across European borders, is one of the union's greatest achievements, and a symbolic indicator of European humanism and liberal tradition. Likewise, there have also been tangible successes with the creation of the *Euro* and the exchange of university students through the *Erasmus programme*. These three achievements constitute signs of identity, as if they were milestones forged through hard work in the invariably challenging route towards the construction of a common Europe. Brexit, on the contrary, signifies a point of inflection in this progressive collaboration to achieve European identity, an uncertain and unexpected interruption in the dream of continental unification.

Brexit signifies a point of inflection in this progressive collaboration to achieve European identity

There is no doubt that Brexit is a product of *Euroscepticism* arising in the last few years, coinciding with the economic recession beginning in 2008. The decision on Brexit also reflects the social wounds generated by the austerity policies imposed during a clumsy management of crisis by European leaders. The solutions that are now being considered contemplate the development of a European Union at different rates, with the obvious risk of deepening the social divide between regions and countries. The feeling of national inequality hinders the aspiration of constructing an authentic European Union, with a unique and powerful voice, capable of establishing itself alongside the US and China.

In addition to the free movement of people, the single currency, and the exchange of university students previously mentioned, another essential constructive European milestone – less known in the public consciousness – is the framework programme for research and innovation, a powerful tool for the promotion and support of scientific research and the development of technology in the EU. The *Horizon 2020 programme*, currently in effect, was preceded by seven framework programmes, of which the first was launched in 1984. Discussions in the European parliament have now started as to

the next framework programme, with a tentative investment of up to 100 billion euros, which will be distributed between 2020 and 2026.

One of the primary objectives of this programme is to promote collaborative investigation throughout Europe and with other partner countries, contributing to the mobility of scientists and business, with the goal of European cohesion in mind. Consequently, the sciences have acquired an extra value, which is more political than scientific in nature, and emerge as a key instrument for the integration of countries into a single Europe. In other words, apart from their indisputable intrinsic value in promoting continental scientific and technical development, the framework programmes also foster high-level professional networking, and hence, trans-national integration of sectors driving the European economy.

> **The sciences have acquired an extra value, which is more political than scientific in nature, and emerge as a key instrument for integration**

We should be conscious, however, that science and technology do not level the playing field as other innovations have done in the past, but instead accentuate the unequal distribution of wealth among social classes as well as nations. It was in the middle of the last century when forward-thinking countries imposed on the rest of the world a model for linear and unidirectional economic progress, based on the financing of science and technological development. The social and environmental consequences of this developmental model remain evident. In fact, the proposal to facilitate the growth of Europe at different rates responds to the economic discrepancies between EU nations, which itself reflects disparities in science and technology development.

Because of this, the European framework programmes must urgently exploit their maximum potential, not only scientifically but also politically. And now, following Brexit, more than ever. The European research and innovation framework programme must today be understood not only as an element of economic progression but also as a cohesive political tool with the potential to combat the dangers of uneven EU development. In this sense, the EU should resist the understandable impulse to break ties with the UK and slam close the door, but to find ways to incorporate the British scientific community into the European integration project. If the Europe of 27 succeeds in achieving the long-awaited goal of political unification, it is not unreasonable to assume that the UK will end up knocking at the door once again.

> **The EU should resist the understandable impulse to break ties with the UK and slam close the door**

Experience tells us that groups advance faster than isolated individuals. Nature is plagued with examples, including common social insects (bees, ants, etc.). The evolution of the human species itself would not have occurred if not for the communal character of man. In fact, the so called *collective intelligence* or *symbiotic intelligence*, resulting from collaboration and competition between individuals that make up a particular group or population, allows for an improved intellectual capacity by exceeding the knowledge of each isolated element. George Pór, whose pioneering research in the 1980's into the development of knowledge networks and the construction of virtual communities involved in self-

organisation, defines collective intelligence as "The capacity of human communities to evolve towards higher order complexity and harmony, through such innovation mechanisms as differentiation and integration, competition and collaboration."

It can be difficult to admit that the driving force of collective intelligence is "individual selfishness", identified by the Scotsman Adam Smith – the father of modern economics – in his seminal work *The Wealth of Nations* (1776) [3]: "It is not from the benevolence of the butcher, the brewer, or the baker that we expect our dinner, but from their regard to their own interest. We address ourselves, not to their humanity but to their self-love, and never talk to them of our own necessities but of their advantages". The Nobel laureate Mario Vargas Llosa recently referred to the work of Smith in the following terms: "In truth, he was the first to explain to human beings how and why the system operates which lead us to leave the caves and progress in all fields – save from the moral – to conquer the content of material and reach for the stars. A simple and yet complex system, founded on liberty, which transforms selfishness into a social virtue" (El País, March 19th, 2017 [4]).

In spite of its many oscillations, the history and social evolution of man is a result of the collective intelligence of a species in which individual selfishness – understood as a social virtue – constitutes the driving force behind the whole, and technoscience – understood in its dual economic and political role – is one of the key levers of action. In this continuous historical development, the construction of the United States of Europe should be no exception.

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Biofísica Magazine

BEYOND BIOPHYSICS

Medical Physics and Biophysics

A conversation with José Bernabéu

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Prof. José Bernabéu,
IFIMED / IFIC, UV

Medicine and physics have always been interconnected. Physics is at the ground of all natural sciences, of which medicine is arguably the most impacting one since health is a priority for people. Advances in physics mean new ways to interpret Nature and often give rise to new concepts and methodologies which allow advances in other branches of science. Among them, medicine enjoys a privileged attraction by physicists. This alone explains the *synergy* between Physics and Medicine, at least during the last century.

In fact, looking back in history, we find that the birth of particle and nuclear physics, which are two landmarks of modern science, gave rise to the development of new medical applications. Thus, medical physics was born and grew, hand by hand, with the understanding and capacity to manipulate radiations, which were employed for medical purposes even before the discovery of their nature. The synergy persists today but with renewed forces and like in the past the thrust comes from new advances in physics, put to the service of human health. Modern medical physics is still based mainly on applications of radiation, but now incorporates different types of it and is used for a variety of clinical purposes, from diagnosis to therapy. The contributions of physics have also expanded. Radiation therapies have evolved to use high energy sources based on protons and ions which combine effectiveness, specificity and very low side effects. Moreover, instruments used for particle detection in modern particle and nuclear physics have been the basis for the development of a new generation of detectors for medical uses which allow in situ non-invasive functional imaging on real time.

> **Rediations were employed for medical purposes even before the discovery of their nature**

Worldwide, top level physics institutions, like CERN and Fermilab, have been and continue being capital for new developments in medicine. A privileged witness and actor of past and recent achievements in medical

physics is José Bernabéu, professor at the *Instituto de Física Corpuscular* – IFIC (University of Valencia and *Consejo Superior de Investigaciones Científicas* – CSIC). As specialist in physics of elementary particles, he has dedicated the last years to the creation of IFIMED (*Instalación de Física Médica*), a unique Facility in Spain meant to explore new methods for treatment and diagnosis of cancer and degenerative diseases using *proton therapy* and including also the development of accelerators, detectors and medical image equipment.

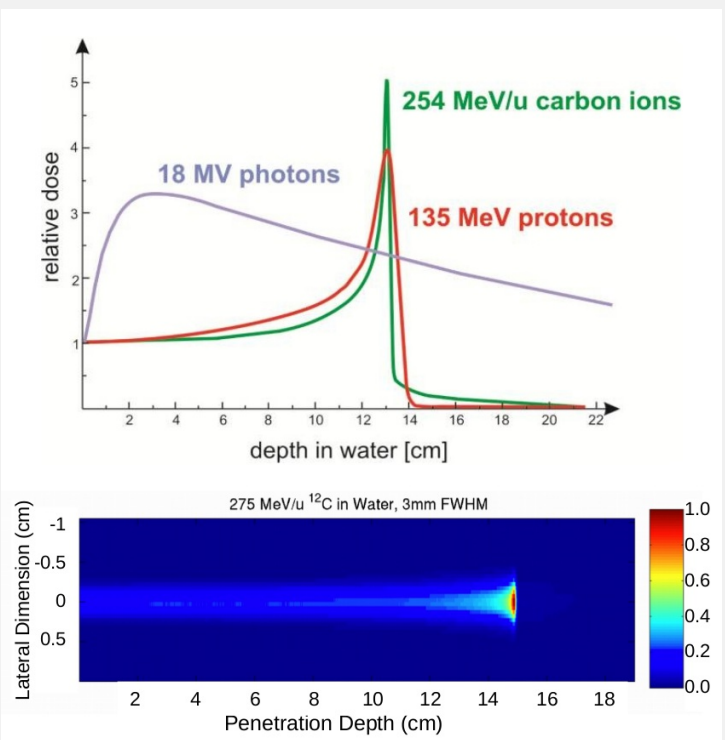
I meet professor Bernabéu for an over-lunch conversation about medical physics and biophysics in the cafeteria of our common campus. A priori, one would probably expect some overlap between the two fields, and I start, quite naïvely, pointing this out to prof. Bernabéu. He has a clear and immediate answer: "There can, of course, be some level of coincidence, like there is between biology and medicine, but you would not mix these two either". Then, I realize throughout the conversation that there are important differences between the two fields: Medical physics works always close to medical problems. Physicists tailor physical phenomena to develop and fine tune new methods, to be used in the clinic. Their end goal is research oriented to cure people and they often work in collaboration with medical doctors and radiophysicists. A fruitful joint environment of research and clinic results in a desirable synergy. Biophysics, in contrast, uses a much broader approach and is more pluridisciplinary because the studies are oriented to all life sciences, not just medicine.

> **"Physicians are more conservative than physicists. That is understandable, but how do you get proofs for something without trying it!"**

> **The cure of cancer has been, and continues to be, the major driving force of medical physics**

The close connection with hospitals and collaboration between physicists and medical doctors are influential characteristics for the development and implementation of medical physics projects. Professor Bernabéu says that "physicists and medical doctors have often different points of view and different ways to solve problems. Their scientific language is also different, which sometimes hinders communication. Physicians are more conservative than physicists. That is understandable, as they are used to work with patients, but how do you get proofs for something without trying it!" Medical doctors base diagnosis and prognosis on recognisable patterns (symptoms) from different types of observations. They are normally very focussed specialists on particular organs or pathologies, but they also must deal the patient as a whole. On the other hand, physicists may not be aware of all the physiological details of the human body and its parts. However, they can represent it as a complex system, made of a hierarchical collection of nested complex sub-systems, from cells to tissues, to organs to the complete organism, and with a list of associated properties, organised as a dynamic network, exhibiting emergent behaviour, with feedback loops and non-linear relationships between parts… "For a physicist cancer is a complex adaptive system, which evolves as a results from the redundancy and multiplicity of subclones and interactions at different scales. Heterogeneity, metastases and evolution towards resistant states can be seen as emergent properties of such a system. This is where biological and physical sciences converge."

The reference to cancer does not come out by chance. In fact, the cure of cancer has been, and continues to be, the major driving force of medical physics. The main outcome has been the development of a variety of therapeutic methods based on the use of radiation and known collectively as radiotherapy. The idea behind these methods is to use a penetrating radiation to eliminate malignant cells. It should be sufficiently energetic to reach the tumour and should ionize molecules which then produce cascading effects and ultimately trigger cell death. But ideally the radiation should have a localized action, like surgery, with no effects on healthy tissues. This seems a complicated issue!



New radiation sources allow conformal dose distributions, which concentrate energy in a reduced volume along the penetration pathway and minimize the effect on healthy tissues. Image courtesy of prof. José Bernabéu.

I ask prof. Bernabéu about the limitations of classical radiotherapy and the solutions introduced by new developments in recent years. "The two requirements, strong power and selectivity, turn out to be difficult to achieve simultaneously." This has limited the use of radiotherapy, depending on the localization and distribution of tumours. Conventional, external radiotherapy nowadays is still based on the use of *X-rays*, mainly produced by linearly accelerated particles (linacs). These are penetrable sources but weakly selective. On the other hand, a classical problem has been the precise localization of the tumours. The introduction of imaging techniques in the 80's allowed the control of the position and size of tumours and to calculate adequate radiation doses. "But an important breakthrough has been the use of beams of accelerated protons and ions (like carbon and neon ions). The advantage is that with these beams the dose keeps low for much of the penetration path and then peaks to reach a maximum at a narrow position which decays steeply from that point. This allows deposition of high energy in a small volume with minimal effects on surrounding areas." Prof. Bernabéu explains to me that the energy maximum corresponds to the Bragg peak of the radiation (see accompaning Figure) and its position can be adjusted to coincide with the position of the tumour.

The phenomenon was well known from early studies with cyclotron accelerators and had been applied to patients already since 1957. However, the use of protontherapy is only extending in recent years. "Nowadays this therapy is possible in more than 30 specialized centres in America, Japan and Europe and there are many others under construction. These are mostly particle physics research laboratories and there are also some installations in hospitals. The ideal site is a joint medical physics

research facility associated to a hospital."

In Spain IFIMED, coordinated by Professor Bernabéu, "has completed in its Phase I the infrastructure for research in Imaging and Accelerators applied to Medicine, and contemplates in its Phase II an accelerator delivering protons up to 230 MeV -MeV is a million of electron-Volts, the eV being the energy acquired by an electron when 1 Volt is applied. This proton accelerator can be used for research and for protontherapy, the Bragg Peak for reaching tumours being located up to 32 cm deep in the human body." He points out that this is not a hospital but a research centre. In parallel, it can also be used for treatment of patients in cases where conventional radiotherapy is either inefficient or inconvenient due to side effects. Professor Bernabéu gives us an example. "Eye tumours, where conventional radiotherapy is of no use because the effect on healthy cells ends up destroying the function of the eye. Other cases are solid resistant tumours, for which it is important to apply concentrated energy in a small area, and early detected isolated tumours." This ambitious project is also conceived as a facility for users and teams up with other projects in Europe. "IFIMED is member of ENLIGHT, the European platform of particle therapy centres for activity in medical physics, coordinated by CERN. This includes other projects like PARTNER, the particle training network of European radiotherapy, ENVISION, the on-line non-invasive monitoring of the application of hadrontherapy to patients (imaging in real time), OMA, the optimization of medical accelerators and OpenMED, the design of a prototype of an ideal accelerator for particle therapy taking advantage of the Bragg Peak."

Detection and imaging are also of the interest of medical physics. The first medical images were based on X-rays but nowadays a variety of types of signals, detectors and mathematical and computerized treatments of data have given rise to a long list of sophisticated imaging methods. Classical imaging provides structural information (form). This, in principle, has also functional importance, since structure and function are correlated at all levels in biology (from molecules to cells to organs). However, modern medical imaging is designed to provide high level functional information, like the spatial distribution of specific molecules in the body. Again, the development and generalization of functional image methods for their use in medicine has a lot to do with advances in physics. Two of them are magnetic resonance imaging (MRI) and positron emission tomography (PET). Although the physical basis of the two methods are very different, in both cases the atoms responsible of the signals are naturally present in the body (hydrogen atoms from water, in the case of MRI) or can be easily incorporated to normal organic molecules (positron emitting isotopes, for the case of PET) and thus the images inform directly about the physical and physiologic (metabolic) state of the tissue.

> **Scientific progress consists mainly in finding the right questions: the answers just follow**

Professor Bernabéu stresses that imaging is not only important for diagnosis. "Detection and imaging can complement protontherapy. With an appropriate detection, imaging can inform in real time about the therapeutic mechanism. For example, cell death triggering may not be due to the direct action of the proton beam but to the effect of secondary electrons ejected from cell molecules as they are hit by the radiation. For this reason, integration of particle acceleration, detection and imaging at IFIMED is an important innovative aspect, not common in other medical physics infrastructures."

Professor Bernabéu is also an enthusiastic defender of basic research: "All great developments originate in basic research, without ever suspecting about their possible applications. This is, for example, how the world-wide-web started at CERN with a purpose very different from that we give it today. It was invented there, not at IBM!". Along the same lines, he also likes to say that scientific progress consists mainly in finding the right questions (the answers just follow). Medical physics is a good example where a few scientific questions pertaining to the field of particle and nuclear physics have yielded a benefit for people as invaluable as curing cancer. Then, I ask him to tell us a question that will motivate medical physics research in the coming years.

> *Protontherapy can be even more efficient with low dose if we know the precise position of the tumour at each moment during the application of the therapy. As we have moving organs, is it possible to integrate Imaging with Therapy in order to monitorize on-line, in real time, both the accelerator energy and the effects of therapy?*

Yes, this is a really big question! I am sure medical physicists will soon provide good answers to it.

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Biofísica Magazine

COOL BIOPHYSICS

Protein aggregation:

Toxicity and function, two sides of the same coin

Salvador Ventura, *IBB-UAB, Barcelona (Spain)*

Protein *misfolding* and aggregation are linked to the onset of more than 40 human diseases. Although protein aggregation is potentially harmful for the cell and usually compromises its fitness, the vast majority of proteins contain sequences that predispose them to aggregate. The reason behind this apparent contradiction is that the presence of such sequences provides a number of structural and functional advantages, as long as they are kept under control.

A growing interest in the study of protein aggregation

The study of protein aggregation has remained for long time as a marginal research topic, restricted to the biotechnological area. Protein aggregates were only of interest as a source of recombinant proteins during the heterologous expression of insoluble proteins and most of the efforts in this field were devoted to find conditions in which they could be refolded to render the maximal yield of native protein, usually via trial and error approaches [1]. The revival of protein aggregation during the last two decades owes to the discovery that this phenomenon underlies a broad range of human pathologies, turning it into one of the most competitive and exciting research areas nowadays.

The number of diseases associated, directly or indirectly, with protein aggregation continues to grow. Perhaps the best known of these disorders are the neurodegenerative disorders, which include among others Alzheimer's, Parkinson's and Hungtinton's diseases, the so-called prion diseases and amyotrophic lateral sclerosis (ALS). The abnormal aggregation of proteins is also behind pathologies like type II diabetes, cardiomyopathies, cataracts or even certain types of cancer [2, 3]. Some of these diseases have a clear genetic origin, but for most of them sporadic cases are the commonest. In some cases, transmission of the disease to healthy individuals has been reported, as in the case of prions. While aggregation-associated diseases can exhibit very different clinical manifestations, they share certain features; for example, they all display a late onset, with symptoms appearing usually in the adulthood, suggesting a common underlying mechanism of toxicity. Understanding the common and

differential features behind these devastating diseases might allow progressing towards finding efficient therapeutic strategies.

Structural properties of protein aggregates

Proteins are the workhorses of the cell, being the final executors of the myriad of activities that sustained life requires. Generally, the polypeptide chains that come out from the ribosome in an unfolded conformation must adopt a defined three-dimensional structure -the *native state*– to be functional. In many cases, when this active conformation cannot be attained or maintained, misfolded proteins tend to self-assemble either intra- or extra-cellularly to build up insoluble deposits [4] (**Figure 1**). The formation of these aggregates promotes loss of protein function, saturates the protein quality control machinery, and leads to aberrant interactions and the subsequent co-aggregation of other essential cellular proteins. Thus, it is not surprising that protein aggregation becomes associated to pathological states. The proteins involved in these disorders do not share any sequential or structural similarity [3]. They can be intrinsically disordered, like α-synuclein in Parkinson, predominantly constituted by β-sheets such as SOD1 in ALS or, alternatively, α-helical like insulin in injection-localized amyloidosis. They can be small and monomeric, like amylin in type II diabetes or big and multimeric like transthyretin in familial polyneurophaty. Protein aggregation contradicts the one sequence / one structure / one function central biology dogma, because, independently of their sequence and native conformation, when these proteins aggregate into their toxic species they all converge to form macromolecular assemblies sharing a common fibrillar architecture, known as *amyloid* fibrils [5].

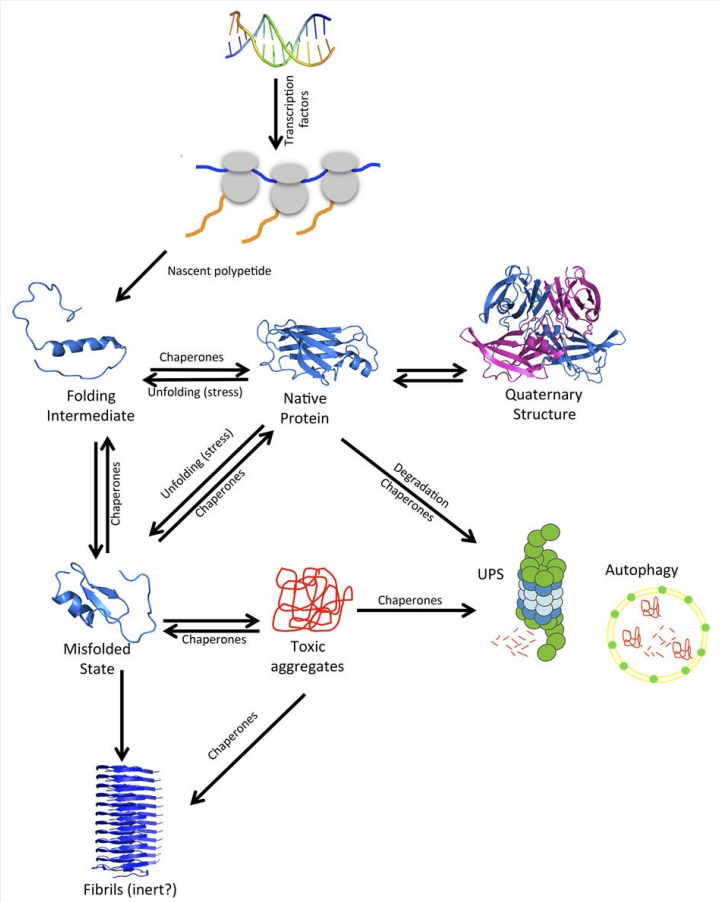

Figure 1. Overview of the proteostasis network (PN). A protein, during and after its synthesis at the ribosome, can adopt many different conformational states on the way to its native 3D structure. Imbalances in proteostasis often lead to protein aggregation and disease. *Reproduced with permission* from Pallarès & Ventura. *Proteomics* 2016, 16: 2570.

Amyloid fibrils are characterized by a polypeptide backbone organization in a cross-β disposition, which consists of a succession of contiguous β-strands stacked perpendicularly to the fibril axis. For many years, the characterization of amyloid fibrils using high resolution structural techniques like solution NMR and X-ray diffraction, remained elusive. Therefore, the presence of these insoluble deposits has been classically inferred from the results obtained using a battery of assays, including

morphological analysis using transmission electron microscopy and atomic force microscopy, staining with amyloidtropic dyes such as Thioflavins and Congo Red, resistance to proteolysis, or checking out the seeding capacity characteristic of amyloid assemblies. Concomitantly, secondary structure analysis by circular dichroism, Fourier transformed infrared spectroscopy, or X-ray diffraction of aligned fibrils has been used to identify the characteristic cross-β-sheet signature in these protein aggregates [6]. Only recently, using short amyloid peptides able to form in the same conditions amyloid fibrils and microcrystals suitable for X-ray crystallography, the structure of the inner regions of amyloids could be studied at atomic resolution. In all cases, as predicted by low resolution techniques, the amyloid-like structures were shown to be formed by densely packed parallel or antiparallel intermolecular β-sheets [7]. However, the high resolution X-ray structure of a complete protein in its amyloid conformation remains to be elucidated. This structural gap has been partially filled by solid-state NMR studies, which exploiting extensive sets of experimental restraints have allowed to delineate the molecular interactions sustaining the amyloid fold in a reduced set of full-length proteins and peptides [8] (**Figure 2**).

Functional proteins cannot avoid aggregation

Contrary to what was initially thought, the phenomenon of amyloid formation is not restricted to a reduced number of proteins involved in disease. Instead, potentially any polypeptide is at risk of aggregation, and, indeed, it seems that ability to self-assemble into amyloid-like structures is an intrinsic property of polypeptide chains [9]. This surprise is not so striking now that we know that the the most stable conformation that a protein can adopt is not the native state, but the highly repetitive and densely stacked amyloid fibril. Hence, amyloid fibrils constitute a thermodynamic sink in which multiple proteins can get trapped [10]]. Indeed, computational studies at large scale indicate that the presence of short sequence stretches with high aggregation propensity is ubiquitous in all the analysed proteomes and some of them tend to be evolutionary conserved [11].

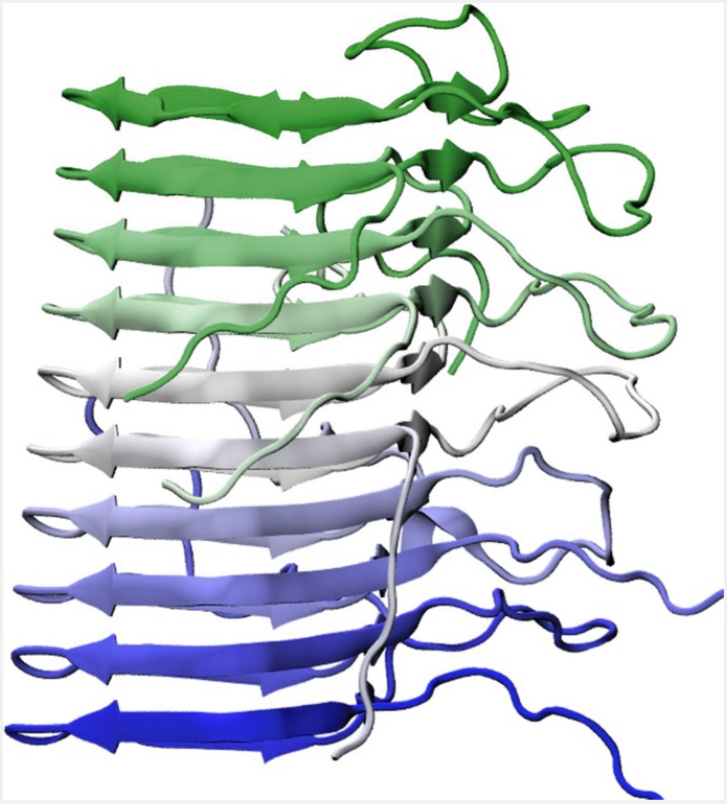

Figure 2. Solid state NMR structure of HET-s in its prionic amyloid conformation. Each individual protein molecule contributes two layers of the β-sheet solenoid. The β-sheets are stacked orthogonal to the fibril axis.

The questions that arise are: If protein aggregation impacts cellular fitness, why natural selection did not purge it out from the population, as it happens with deleterious mutations that impact the properties of structural or functional sites? Is there any benefit in conserving aggregation-prone regions in proteins that explains why is worth to take the risk? We are just beginning to find the

answers to these questions by realizing that the establishment of protein functional interactions and the formation of anomalous contacts leading to the toxic protein aggregates are indeed two sides of the same coin, based on very similar physicochemical properties.

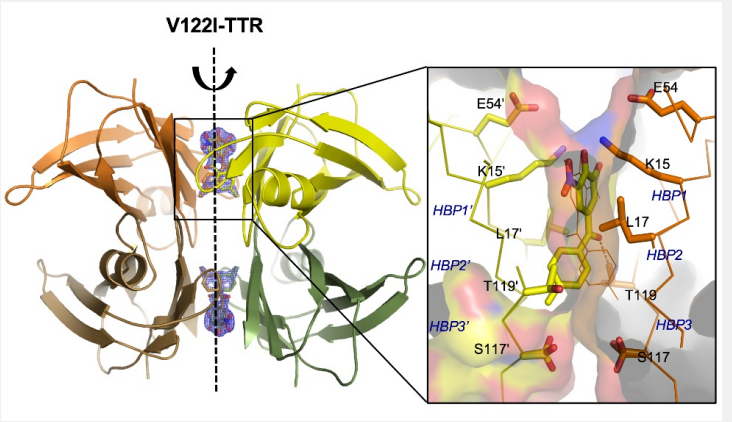

Figure 3. Therapeutics against Transthyretin (TTR) caused amyloidosis. Stabilization of the quaternary structure of a TTR mutant causing cardiomyopathy with chemical chaperones such as Tolcapone prevents protein dissociation, precluding aggregation and eliminating TTR toxicity in cardiomyocytes. *Reproduced with permission* from Sant'Anna, *et al. Nat Commun*. 2016, 7: 10787.

Protein regions with high *aggregation propensity* are usually rich in hydrophobic residues and depleted in charged amino acids. This composition is similar to the one of regions driving the formation of protein hydrophobic cores, which constitutes in many cases the first step of protein folding and whose correct assembly is crucial to maintain the metastable structure of functional proteins. Folding and aggregation kinetically compete in the cell, simply because aggregation-prone regions are essential to fold into functional protein structures in a biologically relevant time frame. This interrelationship is such that, in many cases, when we introduce amino acid changes intended to decrease the aggregation propensity of a given protein, we usually destabilize it or even prevent it to adopt a defined globular structure. We know now that there is a strong selective pressure to reduce the overall aggregation tendency of proteins and that nature has evolved a number of complementary structure- and sequence-based strategies to reduce the aggregation risk [12]. The fact that we still find such potentially dangerous regions in the cores of a large majority of proteins is a clear indication that functional globular proteins cannot avoid carrying a certain *aggregation load* during their lifetimes.

Aggregation-prone regions also play a crucial role in the formation of the quaternary structure of proteins or in the assembly of protein complexes [13]. This can be concluded from the fact that the interfaces between protein subunits display a higher aggregation propensity than exposed surfaces, which have evolved to minimize the aggregation risk by increasing the proportion of polar residues against the hydrophobic ones. Indeed, the presence of exposed hydrophobic residues on a protein surface is usually indicative that they play a functional role, as they have been shown to be more conserved than the rest of the amino acids [14]. Having exposed hydrophobic residues implies an inherent aggregation risk and, unless they serve for a specific purpose, they should have been purged during evolution. The unwanted dissociation of protein quaternary structures into their subunits is associated with the onset of a number of degenerative disorders, like the transthyretin (TTR) caused amyloidosis or ALS, just because the dissociated monomers freely expose aggregation-prone regions previously hidden at the interface, resulting in their fast self-assembly into amyloid like structures. The link between protein dissociation and aggregation provides a therapeutic window to halt the

progression of these diseases. The stabilization of the quaternary structure of these proteins using small chemical compounds, known as *chemical chaperones*, is the only therapy we have nowadays in the market to target a protein aggregation-linked disease [15, 16] (Figure 3).

The prion-like phenomenon: generating revolutionary protein functions

When amyloid fibrils grow and divide with high efficiency they can *propagate* and are then termed prions. These fibrils propagate their conformation in a self-templating process. Prion diseases were thought to be exceptional because the pathology can be transmitted from organism to organism through a protein-based mechanism [17]. However, it is becoming apparent that protein-based propagation may reach beyond the scope of these relatively rare diseases to frequently occurring neurodegenerative disorders, including Alzheimer's and Parkinson's diseases [18]. These findings suggest a unifying mechanism underlying the pathogenesis of neurodegenerative disorders in which protein aggregates can be directly transmitted from pathologically affected to healthy, unaffected cells, thereby potentially extending the disease process throughout the nervous system [19].

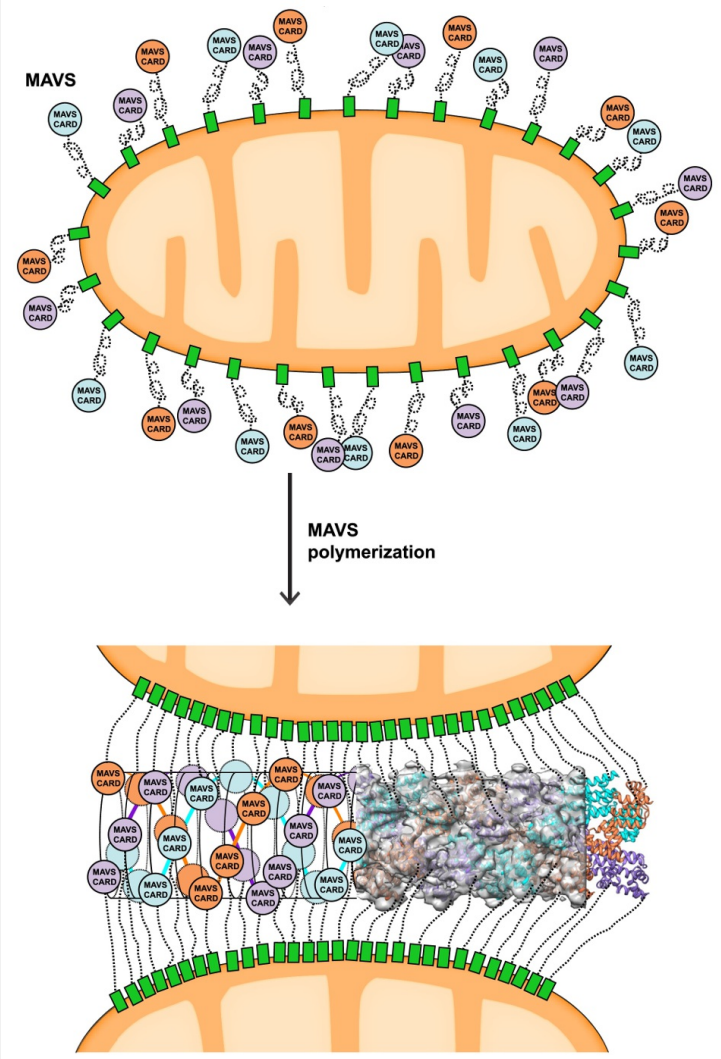

Figure 4. Functional prion-like polymerization in human immune response. The mitochondrial protein MAVS, located on the surface of mitochondrial membranes, polymerizes into functional prion-like aggregates in response to viral infection. These assemblies activate and propagate an innate immune response in a reaction that depends on the recognition of viral RNA by the RIG-1 receptor. *Reproduced with permission* from Xu, H., *et al. eLife* 2014, 3: e01489.

Nevertheless, the traditional association of human prion proteins with disease has overshadowed one of the most interesting and unique attributes of prions: their ability to spontaneously shift between soluble and self-templating aggregated states. It is now clear that this property is exploited for functional purposes by different organisms and underlies some of the most revolutionary new concepts in biology, including protein- based genetic elements, membrane-free compartmentation, evolutionary capacitance and the revelation of cryptic genetic variation [20]. In these processes, typically, the prionic conformation compromises protein functionally, resulting in the expression of new phenotypes, previously repressed by the

presence of the functional soluble conformation. However, for some prion-like proteins, a gain of function occurs and aggregation is used to propagate a biological function. In this way, the prionic conformation of the RNA-binding protein, Cytoplasmic Polyadenylation Element Binding protein (CPEB), displays increased affinity for RNA, contributing to long-term memory formation in metazoans [21]. Similarly, it has been shown that after viral infection, the human mitochondrial protein MAVS forms functional prion-like aggregates responsible for activating and propagating the innate immune response [22] (**Figure 4**). Importantly, protein response to environment based on protein conformational changes is much faster than receptor mediated activation of gene expression. Indeed, computational analyses indicate that prion-like proteins are present in the proteomes of organisms in all kingdoms of life [23], constituting a diverse and amazing group of proteins whose functional relevance would clearly expand beyond their potential link to pathology.

Conclusion

Protein aggregation is sustained because it is necessary to stablish and maintain both functional intra- and inter-molecular interactions. In addition, the formation of highly ordered macromolecular structures and the ability to shift between monomeric and assembled states allows to gain access to functions that are inaccessible to individual proteins. The potential formation of toxic aggregates and the subsequent development of late onset diseases seems to be the price we have to pay for that. The amazing new functions that we are uncovering for aggregated folds suggest that this price is not as high as we have always thought.

Salvador Ventura
Institut de Biotecnologia i de Biomedicina – IBB,
Universitat Autònoma de Barcelona – UAB, Barcelona (Spain).

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19. Stopschinski BE, Diamond MI. "The prion model for progression and diversity of neurodegenerative diseases". *Lancet Neurol*, **2017**, 16: 323. DOI:10.1016/S1474-4422(17)30037-6.
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Biofísica Magazine

NEWS

Juan Carmelo Gómez-Fernández elected new Secretary General of IUPAB

BY BIOFISICA · 12/09/2017

In elections held during the General Assembly of the International Union of Pure and Applied Biophysics – IUPAB, on **18th July 2017**, within the context of the 19th IUPAB and 11th EBSA congress (Edinburg, UK), Dr. Juan Carmelo Gómez-Fernández was elected Secretary General.
Dr. Gómez-Fernández is professor at the Unversity of Murcia (Spain). He has been President ofSBE and at present he is Treasurer of the Latin American Federation of Biophysical Societies – LAFeBS.

During the same General Assembly of IUPAB Dr. Marcelo Morales, from Brazil, took office as new President and Dr. John Baenziger from Canada was elected Treasurer.

A new Council of IUPAB was also elected with members Silvia del Valle-Alonso (Argentina), David Crossman (New Zealand), Erik J. Dufourc (France), Hans Joachim Galla (Germany), Hiroyuki Noji (Japan), R. Daniel Peluffo (Uruguay), Peter Pohl (Austria), Ksenija Radotic (Serbia), C. Mohan Rao (India), Bryan T. Sewell (South Africa), Frances Separovic (Australia) and Giuseppe Zucchelli (Italia).

Biofísica Magazine

EVENTS / MEETINGS / NEWS

6th Iberian / 10th Iberoamerican Biophysics Congress

BY BIOFISICA · PUBLISHED 01/10/2017 · UPDATED 01/10/2017

6th International Iberian Biophysics Congress and *10th Iberoamerican Congress of Biophysics*.
June 20 – 22, 2017, Castellón (Spain).

Presentation

On behalf of the Organizing Committee, it is my pleasure to invite you to attend the *6th International Iberian Biophysics Congress* and *X Iberoamerican Congress of Biophysics*. This international conference has a tradition of almost two decades. The 2018 edition is organized under the auspices of the Spanish Biophysical Society – SBE, the Portuguese Biophysical Society – SPBf and the Latin American Federation of Biophysical Societies – LAFeBS.

IIBC-2018 will be held in Castellón (Spain) on 20-22 June 2018, in the campus facilities of Universitat Jaume I.

The scientific program includes several Plenary Lectures, as well as Parallel Symposia on selected topics covering the main research areas of Biophysics. Symposia will host invited talks and also short communications selected from submitted abstracts with preference for young researchers. Following the tradition of previous Meetings, a New and Notable Workshop will take place in the morning of the first day. The organizers are committed to make the Poster Sessions a place for networking and the occasion of fruitful and lively discussions in a relaxed atmosphere. Reduced registration fees will apply to participants who are SBE members. Moreover, a number of grants sponsored by SBE and SPBf will be available to encourage young researchers' participation.

Looking forward to seeing you in Castellón.

Best regards,

Vicente Aguilella, Chair of the Organizing Committee

Deadlines

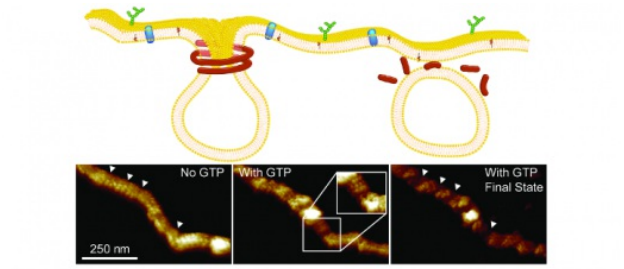
- Bursaries Application: February 20th 2018.
- Early Registration (low fee): March 23rd 2018.
- Abstract Submission: April 15th 2018.
- Late Registration: June 20th 2018.

More information

Please, visit the Congress Web Site.

Biofísica Magazine

PAPERS OF THE MONTH BY SBE MEMBERS: MAY - AUGUST 2107



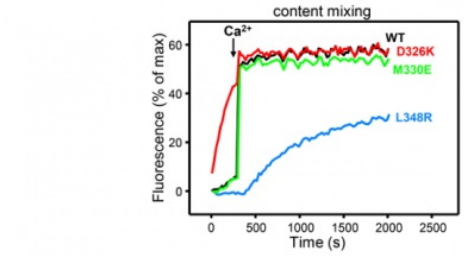
Colom...Scheuring {*Proc Natl Acad Sci USA* 114: 5449}

HIGHLIGHTS 2017 / MAY 2107

Dynamic remodeling of the dynamin helix during membrane constriction

Colom A, Redondo-Morata L, Chiaruttini N, Roux A, Scheuring S.

Proc Natl Acad Sci USA 2017 May; 114: 5449.



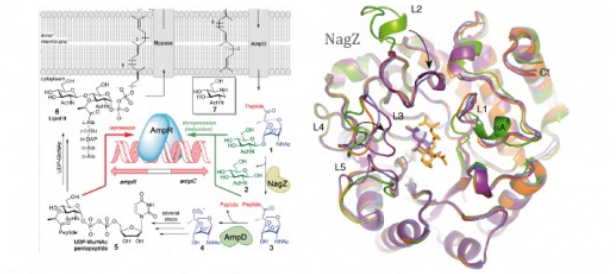
Sitarska...Rizo {*eLife* 6: e24278}

HIGHLIGHTS 2017 / MAY 2107

Autoinhibition of Munc18-1 modulates synaptobrevin binding and helps to enable Munc13-dependent regulation of membrane fusion

Sitarska E, Xu J, Park S, Liu X, Quade B, Stepien K, Sugita K, Brautigam CA, Sugita S, Rizo J.

eLife 2017 May; 6: e24278.



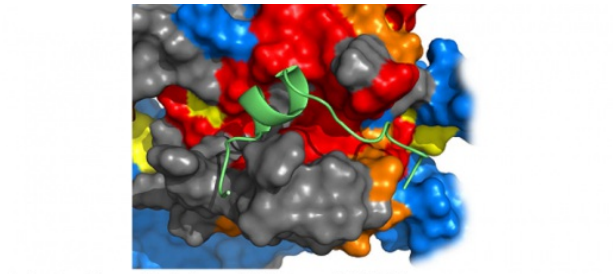
Acebron...Hermoso, Mobashery {*J Am Chem Soc* 139: 6795}

HIGHLIGHTS 2017 / MAY 2107

Catalytic Cycle of the N-Acetylglucosaminidase NagZ from Pseudomonas aeruginosa

Acebron I, Mahasenan KV, De Benedetti S, Lee M, Artola-Recolons C, Hesek D, Wang H, Hermoso JA, Mobashery S.

J Am Chem Soc 2017 May; 139: 6795.



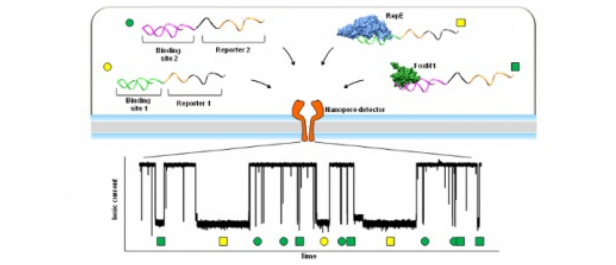
de Opakua...Blanco, Garcia-Marcos {*Nat Commun* 8: 15163}

HIGHLIGHTS 2017 / MAY 2107

Molecular mechanism of Galphai activation by non-GPCR proteins with a Galpha-Binding and Activating motif

de Opakua AI, Parag-Sharma K, DiGiacomo V, Merino N, Leyme A, Marivin A, Villate M, Nguyen LT, de la Cruz-Morcillo MA, Blanco-Canosa JB, Ramachandran S, Baillie GS, Cerione RA, Blanco FJ, Garcia-Marcos M.

Nat Commun 2017 May; 8: 15163.



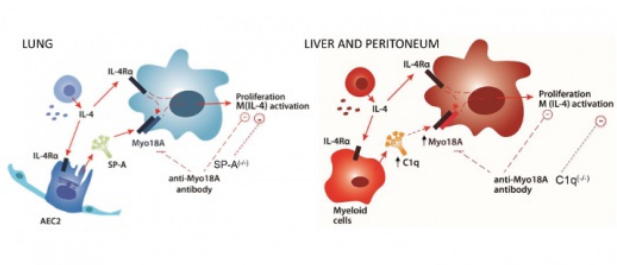
Celaya...Muga, Moro, Rodriguez-Larrea {*ACS Nano* 11: 5815}

HIGHLIGHTS 2017 / JUN. 2017

Label-Free, Multiplexed, Single-Molecule Analysis of Protein-DNA Complexes with Nanopores

Celaya G, Perales-Calvo J, Muga A, Moro F, Rodriguez-Larrea D.

ACS Nano 2017 Jun; 11: 5815.



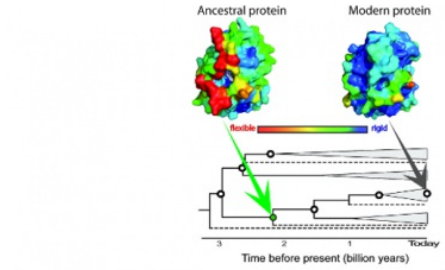
Minutti...Casals, Allen {*Science* 356: 1076}

HIGHLIGHTS 2017 / JUN. 2017

Local amplifiers of IL-4Ralpha-mediated macrophage activation promote repair in lung and liver

Minutti CM, Jackson-Jones LH, Garcia-Fojeda B, Knipper JA, Sutherland TE, Logan N, Rinqvist E, Guillamat-Prats R, Ferenbach DA, Artigas A, Stamme C, Chroneos ZC, Zaiss DM, Casals C, Allen JE.

Science 2017 Jun; 356: 1076.



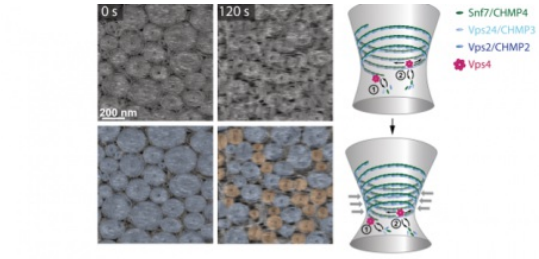
Risso...Sánchez-Ruiz {*Nat Commun* 8: 16113}

HIGHLIGHTS 2017 / JUL. 2017

De novo active sites for resurrected Precambrian enzymes

Risso VA, Martinez-Rodriguez S, Candel AM, Kruger DM, Pantoja-Uceda D, Ortega-Munoz M, Santoyo-Gonzalez F, Gaucher EA, Kamerlin SCL, Bruix M, Sanchez-Ruiz JM.

Nat Commun 2017 Jul; 8: 16113.



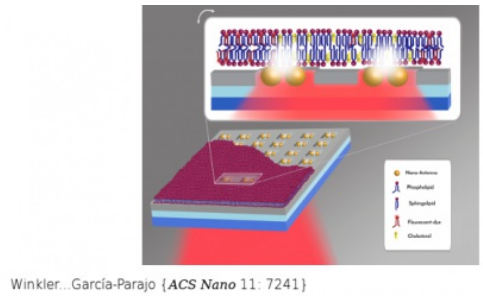
Mierzwa, Chiaruttini, Redondo-Morata...Gerlich {*Nat Cell Biol* 19: 787}

HIGHLIGHTS 2017 / JUL. 2017

Dynamic subunit turnover in ESCRT-III assemblies is regulated by Vps4 to mediate membrane remodelling during cytokinesis

Mierzwa BE, Chiaruttini N, Redondo-Morata L, von Filseck JM, Konig J, Larios J, Poser I, Muller-Reichert T, Scheuring S, Roux A, Gerlich DW.

Nat Cell Biol 2017; 19: 787.



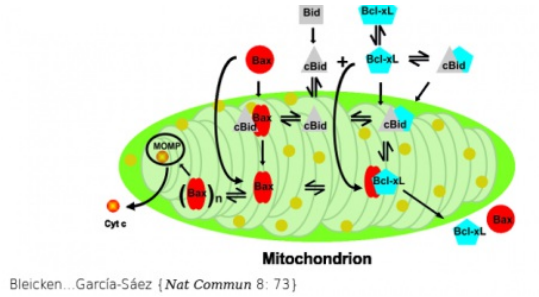
Winkler...García-Parajo {*ACS Nano* 11: 7241}

HIGHLIGHTS 2017 / JUL. 2017

Transient Nanoscopic Phase Separation in Biological Lipid Membranes Resolved by Planar Plasmonic Antennas

Winkler PM, Regmi R, Flauraud V, Brugger J, Rigneault H, Wenger J, Garcia-Parajo MF.

ACS Nano 2017 Jul; 11: 7241.



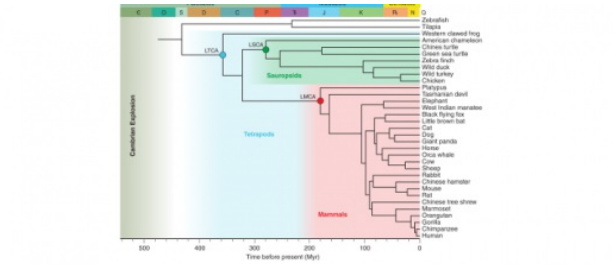
Bleicken...García-Sáez {*Nat Commun* 8: 73}

HIGHLIGHTS 2017 / JUL. 2017

Quantitative interactome of a membrane Bcl-2 network identifies a hierarchy of complexes for apoptosis regulation

Bleicken S, Hantusch A, Das KK, Frickey T, Garcia-Saez AJ.

Nat Commun 2017 Jul; 8: 73.



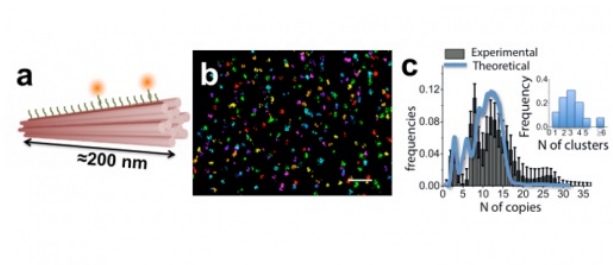
Manteca...Pézez-Jiménez {*Nat Struct Mol Biol* 24: 652}

AUG. 2017 / HIGHLIGHTS 2017

Mechanochemical evolution of the giant muscle protein titin as inferred from resurrected proteins

Manteca A, Schonfelder J, Alonso-Caballero A, Fertin MJ, Barruetabena N, Faria BF, Herrero-Galan E, Alegre-Cebollada J, De Sancho D, Perez-Jimenez R.

Nat Struct Mol Biol 2017 Aug; 24: 652.



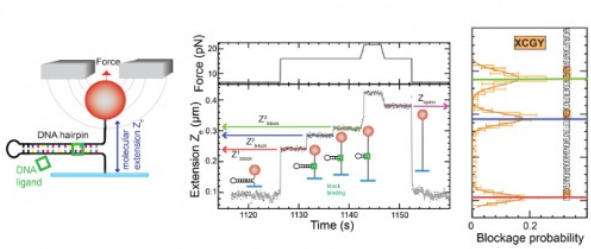
Zanacchi...Lakadamyali {*Nat Methods* 14: 789}

AUG. 2017 / HIGHLIGHTS 2017

A DNA origami platform for quantifying protein copy number in super-resolution

Zanacchi FC, Manzo C, Alvarez AS, Derr ND, Garcia-Parajo MF, Lakadamyali M.

Nat Methods 2017 Aug; 14: 789.



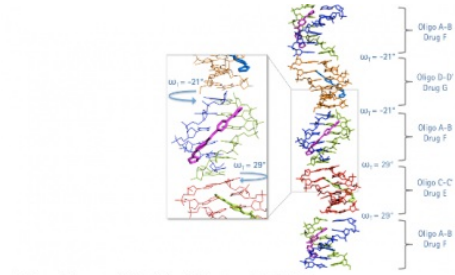
Manosas...Ritort {*Nat Commun* 8: 304}

AUG. 2017 / HIGHLIGHTS 2017

Single molecule high-throughput footprinting of small and large DNA ligands

Manosas M, Camunas-Soler J, Croquette V, Ritort F.

Nat Commun 2017 Aug; 8: 304.



Millán...Campos {*Nucleic Acids Res* 45: 8378}

AUG. 2017 / HIGHLIGHTS 2017

Functional and structural analysis of AT-specific minor groove binders that disrupt DNA-protein interactions and cause disintegration of the Trypanosoma brucei kinetoplast

Millan CR, Acosta-Reyes FJ, Lagartera L, Ebiloma GU, Lemgruber L, Nue Martinez JJ, Saperas N, Dardonville C, de Koning HP, Campos JL.

Nucleic Acids Res 2017 Aug; 45: 8378.

Biofísica Magazine

EVENTS: UPCOMING MEETINGS, COURSES AND WORKSHOPS

EVENTS / MEETINGS / NEWS

6th Iberian / 10th Iberoamerican Biophysics Congress

6th International Iberian Biophysics Congress and 10th Iberoamerican Congress of Biophysics. June 20 – 22, 2018, Castellón (Spain). Presentation On behalf of the Organizing Committee,...

EVENTS / MEETINGS

The Heart by Numbers: Integrating Theory, Computation and Experiment to Advance Cardiology

Biophysical Society Thematic Meeting September 4-7, 2018, Berlin, Germany. Deadlines May 7th, 2018. Abstract submission June 4, 2018. Early bird registration The focus on mathematical...

EVENTS / MEETINGS

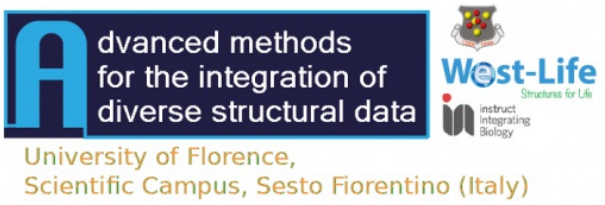
62nd BPS Annual Meeting

2018 Biophysical Society Annual Meeting. February 17 – 21, 2018, San Francisco, California (USA). Deadlines January 15, 2018. End of early registration October 2, 2017....

EVENTS / MEETINGS

IUBMB Focused Meeting on Molecular Aspects of Aging and Longevity

October 16 – 19, 2017, Athens (Greece). Deadlines May 1st, 2017. Abstract submission May 1st, 2017. Fellowships June 1st, 2017. Early registration Aging is an...



COURSES / EVENTS

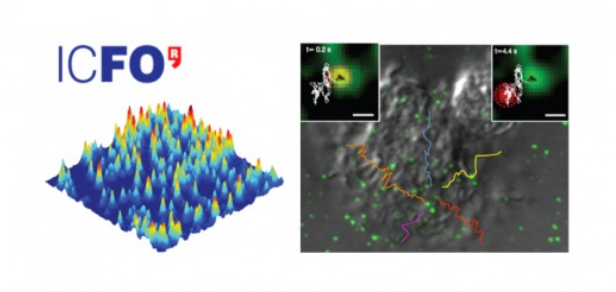
INSTRUCT course: Advanced methods for integration of diverse structural data

February 19th – 25th, DEADLINE for application: November 15th, 2017 AIM: The course aims at training young researchers in the combined use of data from various structural techniques, such...

Biofísica Magazine

JOBS: POSITIONS IN BIOPHYSICS

>



JOBS / POSTDOC

Postdoctoral research position in quantitative fluorescence nano-imaging & single molecule dynamics

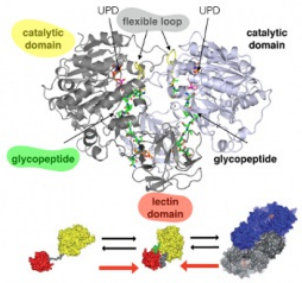
ICFO – The Institute of Photonic Sciences in Barcelona, Spain is offering a Postdoc to a highly-motivated candidate who wishes to enhance his/her scientific career...

BIOFISIKA
Basque Centre for Biophysics

CALLS / JOBS / NEWS

Open position for Scientific Director of Biophysics Research Center, Scientific Park, Biscay

DEADLINE: October 16th, 2017. Biophysics Research Center is a science institute in frontier research and translational excellence at a molecular and cell level in the...



CALLS / FELLOWSHIPS / FPI

FPI-MINECO predoctoral fellowship at University of Zaragoza (BIFI)

The Spanish Ministry of Economy and Competitiveness – MINECO offers a predoc fellowship (former FPI) to carry out a PhD Thesis on “GalNAc-Ts molecular recognition...

JOBS / POSTDOC

Postdoctoral Position – Animal Models of Heart Disease – CNIC (Madrid)

The laboratory of Molecular Mechanics of the Cardiovascular System led by Dr. Jorge Alegre-Cebollada at the National Center for Cardiovascular Research – CNIC in Madrid,...