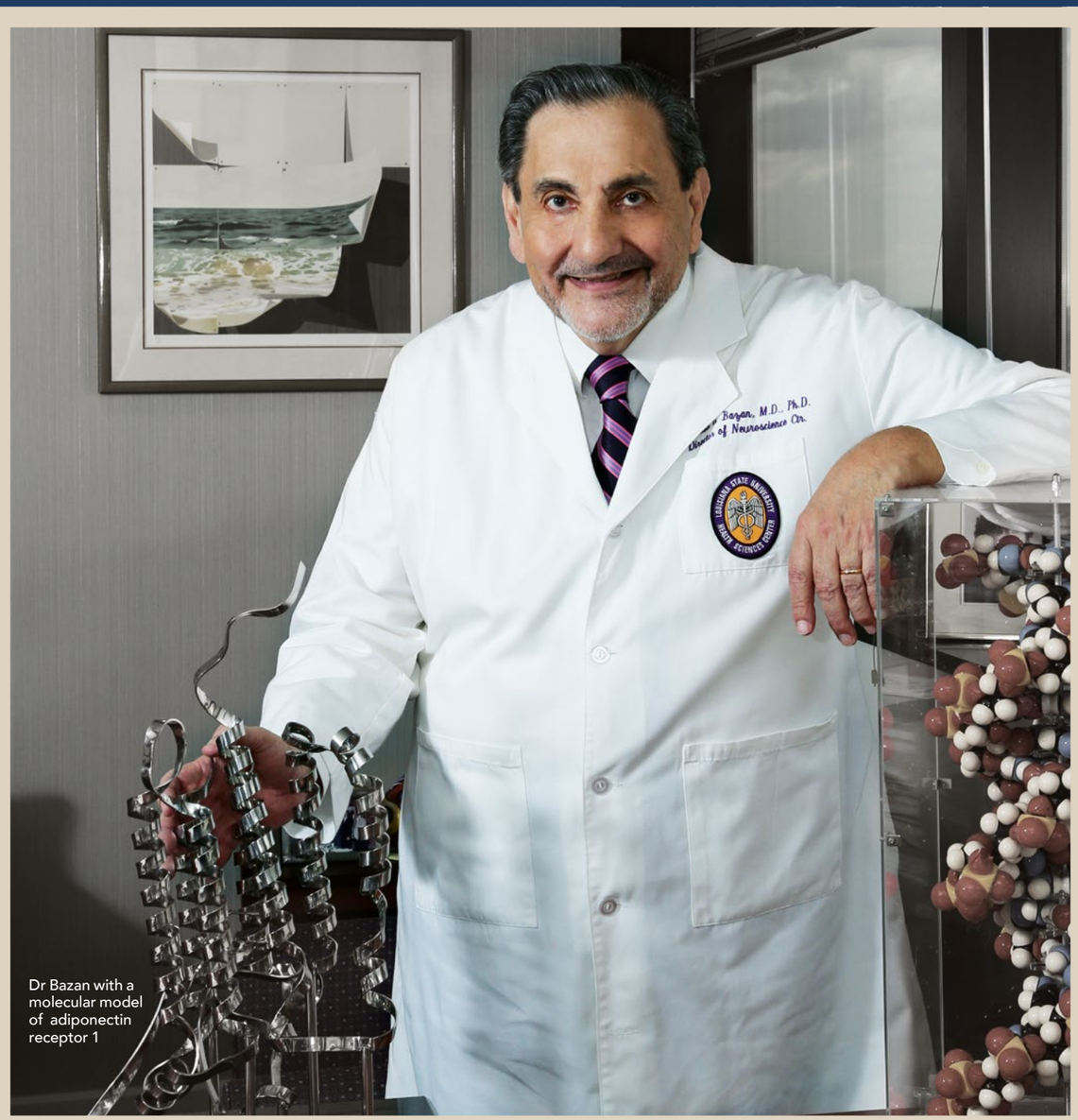


Dr Bazan with a molecular model of adiponectin receptor 1

A marvellous mind

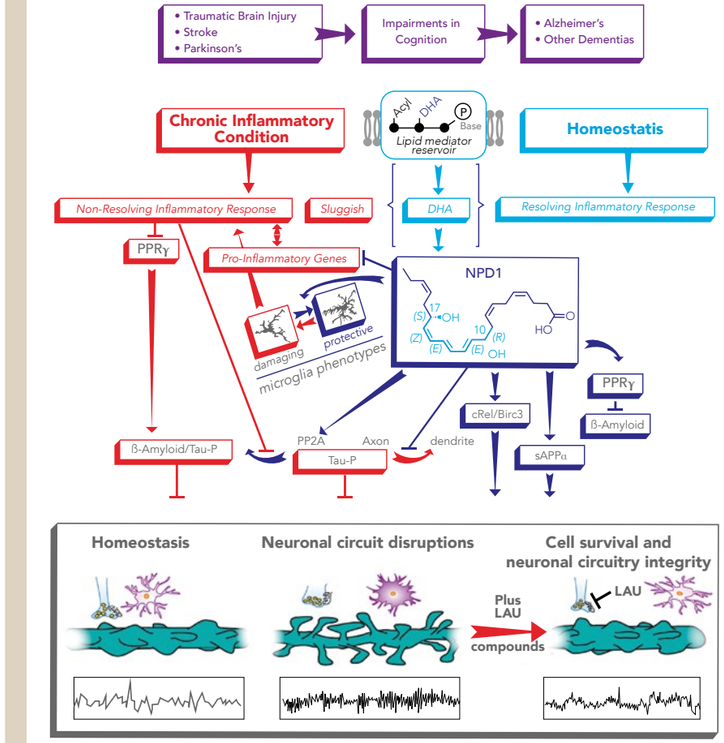
Dr Nicolas Bazan of Louisiana State University Health New Orleans, School of Medicine (LSU) has spent a lifetime uncovering fundamental neurobiological processes, identifying early instructive signals as disease modifiers for neurodegenerative diseases and transforming academic medicine, becoming a household name to thousands of neuroscientists. However, like the great thinkers of history it doesn't stop there, he has also found the time and talent to write books, make a film, mentor the next generation, patronise the arts and lead communities forward with his fresh ideas.

Dr Bazan has featured in so many magazine articles, from *Forbes* to his local *New Orleans Living*, that his background and upbringing is almost a matter of public knowledge. Born in Los Sarmientos, Tucuman province, Argentina, it was in Tucuman City that he studied medicine. Drawn to this subject after experiencing first-hand the chilling effects of neurological disease in his family, he completed his training at Harvard Medical School after a year's stint in New York's Columbia University College of Physicians and Surgeons.

Those who witnessed him achieve selection to the faculty of the University of Toronto at the age of twenty-six must have known he was destined for great things. From here he moved back to his home country of Argentina where he became the founder of the Instituto de Investigaciones Bioquimicas. He also set up a graduate programme in biochemistry and assembled a large group of students and fellows to work in his newly established lab. With exceedingly limited equipment and resources, he struck on two budgetarily feasible ideas: using early amphibian (toad) development as a model of cellular membrane biogenesis and using the retina to study the brain – a decision that would prove enormously beneficial to his work. This productive period was, however, cut short in the early 80s by the political turbulence in the country. In fear of his safety, Dr Bazan was forced to leave his successful institute and flee with his family back to the United States.

The move to LSU quickly followed, where a few years later he was asked to become the founding Director of the Neuroscience Center of Excellence. There he certainly found his scientific home, but it is as likely also that his long stay is due to the finding of a different satisfaction in the cultural melting pot of New Orleans. He credits his faith and family, along with the strong relationships he has built with many around him, as the grounding force that has helped him overcome the hurdle of sudden displacement and other setbacks, among them his triumphal bout against advanced inoperable cancer 14 years ago. Dr Bazan celebrates rather than laments the difficulties he has faced, saying 'adversities bring strength and renewed perspective'.

His awards, honours and collaborations make for a very long list, so long that no one seems to have the time or space to publish it in full. From membership of editorial boards across Europe and the American continent, to chairs, elected to Academic Societies and fellowships of distinguished faculties in the United States (US) and further afield; Dr Nicolas Bazan is a name synonymous with first-class neuroscience research. As Michael Moskowitz, Professor of Neurology at Harvard Medical School/Massachusetts General Hospital puts it, he 'is passionate about everything he does in life, especially his science, and this passion has driven a lifetime of discoveries that have inspired both his students and colleagues'.



THE MAN OF SCIENCE

Dr Bazan focuses his attention not on the lucrative or straightforward cases, but on those neurodegenerative diseases for which there is no known cure. It is perhaps even more telling therefore, that he has made such inroads into the understanding of the underlying pathology. Considering the difficulty of establishing treatments for such diseases, it is no wonder that Dr Bazan himself believes that, 'the only way to conquer them is by getting a new understanding of the cellular and molecular mechanisms engaged in the onset and early progression of brain and retina disease'. This has been his focus during a lifetime of research, a labour which he says he has been, 'lucky to have been able to contribute to'.

Here again the list just goes on and on. There have been breakthroughs in the understanding of the response to the foremost causes of long-term disability in the US – cerebral ischemia (stroke) and seizures (as in epilepsy) – the mechanism of which is now known as the Bazan Effect (as ▶

Dr Bazan focuses on those neurodegenerative diseases for which there is no known cure

Bengt Samuelsson, a Swedish researcher and Nobel Laureate at the Karolinska Institutet in Stockholm, defines it, 'the Bazan effect is the release of polyunsaturated fatty acids during seizures and ischemia'). There is the identification of targets for novel therapeutics, and the uncovering of the novel compounds themselves, to combat the onset and progression of epilepsy; a condition which 30% of US patients do not have adequate control over. Or you can point to the identification of a novel protective molecule to hopefully slow the onset of Alzheimer's disease. Dr Bazan has also targeted chronic pain by developing a novel generation of non-addictive, non-toxic analgesics (painkillers), which he is bringing to market via a new start-up company he co-founded specifically for this purpose, using the findings from his work on injury and inflammation of the brain.

His work has been recognised by distinguished colleagues around the world. Dr George Carman, Chief Scientific Officer at the New Jersey Institute for Food, Nutrition, & Health, Rutgers University, says Dr Bazan, 'has dedicated his career to conducting the highest level of science to the underpinnings of brain function and diseases'. His work has also included a related and equally challenging area, blindness caused by retinal degeneration, and once again he is bringing his experience and intellect to bear with stunning effect.

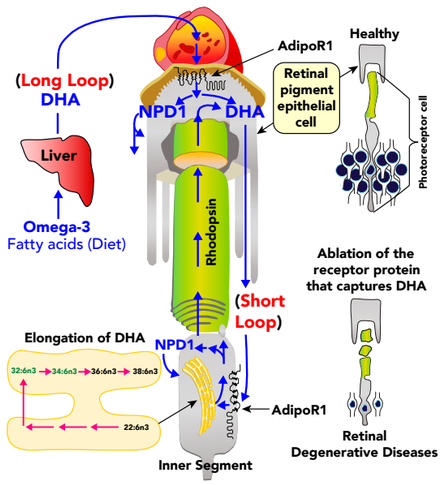
(Left) Dr Bazan has been married to Dr Haydee Bazan for over 50 years; she leads research on cornea nerve repair and regeneration. (Centre) Nicolas Bazan lab members, administrative support and technical personnel of the Neuroscience Center of Excellence. (Right) With artist Taryn Möller Nicoll.

A MAN CAN BE KNOWN BY HIS EYES

The focus of Dr Bazan's work from its discovery at the earliest stage in his career is the brain release of arachidonic acid and docosahexaenoic acid (DHA) upon stimulation. DHA is an omega-3 fatty acid, the precursor of which is only available from dietary sources, and is retained in higher levels in the brain and retina than any other body tissue. DHA is a key component of membranes engaged in brain and retinal function, acting at the junction between brain cells known as the synapse, and in retina photoreceptors. This molecule has been the subject of intense study by Dr Bazan and his colleagues.

The systems employed by the team have been many and varied, but it was during their use of the retina (the light-sensing part of the eye directly linked to the brain) as a model for research on neurones that DHA's role, particularly that of bioactive derivatives, in retinal function and disease was established. Using this approach, they uncovered the mechanism by which DHA is accumulated in the differentiated neurones, the photoreceptor cells, having been absorbed from the diet. Dr Bazan postulated and then demonstrated both the 'long loop' of transport from the liver to the brain and retina, as well as a 'short loop' by which this fatty acid is recovered back to replenish the cells of the retina. This process assured the Bazan team of DHA's status as a key molecule in normal neural function.

They then went on to further elucidate the fate of this molecule as it is first cleaved and then modified by a range of enzymes to produce bioactive docosanoids, molecules which are now known to promote homeostasis and neuroprotection (maintenance and repair respectively). One such of these was named Neuroprotectin D1 (NPD1) because of its role in fostering homeostasis, inhibiting uncompensated inflammatory signals and preventing apoptosis (programmed cell death) as well as other forms of cell death. The discovery that the availability of this potent molecule is decreased, along with its precursor DHA and the enzyme that makes one from the other, in the brain memory areas from early stage Alzheimer's Disease (AD) patients in particular, convinced Dr Bazan and his colleagues that its presence is likely essential in preventing the onset of neurodegeneration. As the retina photoreceptors which provide the stimuli for sight are a type of differentiated neurone, it seems logical that a substance that prevents the death of neurones in AD could also be involved in age-related macular degeneration (AMD), the loss of sight associated with retinal cell death, as well as other inherited retina degenerations. Dr Bazan has led the way in describing the complex interplay of molecules involved in the management of homeostasis in retinal cells, particularly the retinal pigment epithelium (RPE) which is the layer of cells nourishing and sustaining the retinal visual cells. His work is so important it has been described by Prof Joan Miller, Professor and Chair of Ophthalmology at Harvard Medical School, as, 'a lasting contribution to our understanding of the role of lipids in the retina, especially their function as modulators of neuroinflammation, which is the basis of so many ocular diseases'.



Long loop (liver to retina) and short loop (RPE to photoreceptors and back) for DHA conservation. NPD1 is made on demand, when uncompensated oxidative stress arises. DHA is elongated in the inner segments making the key components for photoreceptors' function. AdipoR1 is necessary for vision: it captures DHA and establishes neuroprotection instruction cascades. Its genetic ablation or mutation leads to retinal degenerative diseases (e.g., autosomal dominant retinitis pigmentosa or some forms of AMD).

THE RENAISSANCE MAN

Dr Bazan's most recent research is just the latest in a lifetime of discovery. Bengt Samuelsson describes him as, 'a leading neuroscientist and eye researcher' and points to his work on the Bazan effect, showing that his influence is truly international. However, all his colleagues attest to knowing someone whose intellect is not constrained to a single subject, who has made as much of a mark in the other aspects of his varied life as he has in the scientific community. Prof Edmond Fischer, Nobel Laureate and Professor Emeritus of Biochemistry at the University of Washington says, 'What impresses me most about Nicolas is his enduring enthusiasm and passion, not only for science, but for all of the wonderful things life has to offer. He is the epitome of the renaissance scholar.'

Dr Bazan demonstrated both the 'long loop' of transport from the liver to the brain and retina, as well as a 'short loop' by which DHA is returned to the retina

Harnessing the power of the arts

Dr Bazan has, in addition to his successful scientific career, embraced the arts with equal success. His two published novels (and there are more waiting for publication) follow the life of a neuroscientist. One of these, *Una Vida: A Fable of Music and the Mind* has been made into a compelling and poignant movie *Of Mind and Music* – a process that Dr Bazan was involved in throughout.

The film traces the encounter between a successful neuroscientist and a captivating street musician with Alzheimer's disease. For Dr Bazan, the act of taking his deep knowledge of the world of neuroscience and translating that into a thought-provoking narrative has created a very powerful tool: 'I wanted to contribute to removing the stigma of mental illness in society, because mental illness of any kind is just a disease. I wanted also to create awareness about Alzheimer's disease, and in a way convey a message of hope that science may actually conquer this disease one day.'

'In art it's the same', says Dr Bazan, 'because one can, in an oil painting, illustrate the beautiful, and yet sad, chaos that happens in the brain during Alzheimer's disease.' His dialogue with brilliant artist Taryn Möller Nicoll during her residency at LSU Neuroscience Center of Excellence has led her to create a visually arresting portrait of the degenerative processes that occur in the brain.

With the tools of writing and art up his sleeve, Dr Bazan is lifting the unseen neurodegeneration that underlies so many conditions into the light.

Micromanipulator to isolate single neurones, astrocytes and photoreceptor cells to decipher the transcriptome in early stages of diseases: (from left) William Gordon, PhD, and Jonathan Fuerst (4th-year LSU Health School of Medicine medical student) with Dr Bazan

Q&A

What first piqued your interest in neuroscience?
Well, it was a very early childhood experience that I had. I was six or seven years old and an aunt was taking me to a piano lesson. To make a long story short, she had an epileptic seizure on the street. It was a very traumatic experience to me – all the piano books flew into the air due to a *grand mal* seizure. My mother told me that my aunt, her sister, had epilepsy which was a brain disease, and that stuck in my mind. It was not something that I always thought about but very likely, on reflection, that motivated me to go to medical school and to become interested in the brain and neuroscience.

Later on, my mother strongly encouraged me towards medicine. She really stimulated me to read and to think about medicine, and her message was that by doing something in the medical field I could help people with diseases that were very difficult to cure or to treat.

And a lot of your work relates to neurodegenerative diseases. How did you become interested in them?
Well, it started with epilepsy. During my time at Harvard Medical School I was a fellow at a laboratory, at the Massachusetts Mental Health Centre. This was a psychiatric hospital with a major research effort. I was very impressed by a therapy that was being used intensively at that time, we're talking about the mid-60s, which was electroconvulsive therapy or electroshock. That was, and still is, a treatment used for people who had forms of depression that were refractory to all other medical treatments. One of the things that electroconvulsive therapy does is triggers seizures in patients. And in my mind, I began putting together those early thoughts, or experiences, or connections with epilepsy, and how electroshock might modify or rectify brain chemistry.

I moved to my first faculty appointment at the Department of Biochemistry, University of Toronto, and I was very lucky to be appointed assistant professor at a very early age and Assistant Director of the Neurochemistry Section of the Clarke Institute of Psychiatry. I was 26 years old and again I continued my interest in how experimentally produced seizures would change brain chemistry. So my very first connection was epilepsy and also at that time I began exploring how ischemia, the shortage of blood to the brain often as a result of stroke, also produces these changes.

Your work on experimental seizures and stroke led to the Bazan Effect being named after you. Could you briefly explain what the Bazan Effect is?
I was trying to identify specific chemical changes in the brain due to seizures or to shortage of blood, of ischemia. And I found the release of two types of essential fatty acids, omega-6 and omega-3. The long names are arachidonic acid and docosahexaenoic acid.

Essential fatty acids are so-called because our body is unable to make them. We have to get them or their precursors from the diet. Arachidonic acid goes all over the body to all the tissues, but the other one, docosahexaenoic acid, goes mainly to the brain and to the retina, that is, to the nervous system. Both become part of the structure of the cells. And at that time we didn't know that an acute event like a seizure or ischemia would trigger the release of these fatty acids in tiny amounts. Release means that the chemical connections that they have in the membranes are broken and then they become free fatty acids.

So, I developed methods to identify this and what was surprising was that the speed of release was very, very high. So the idea was, is this a post-mortem phenomenon? Is this something pathological? Or is this event related to function? And looking at the electroshock experiments that I did at that time, in fact what we found is that once the fatty acids were released, after the shock was over they came back into the membrane. So, it was a reversible phenomenon and that suggested that this was linked to function. Thereafter we found a connection between what happens during seizures, and what happens when the brain develops neurodegenerative diseases.

Can you explain the role of these two fatty acids in a healthy nervous system? What do they do normally?
Well the first one, arachidonic acid was shown to be the precursor of prostaglandins and many other important mediators that were discovered by Professor Bengt Samuelsson at the Karolinska Institutet. Because these mediators have 20 carbon atoms, they are called eicosanoids.

When I moved to New Orleans in the very early 80s, in my laboratory we obtained evidence that perhaps DHA may also be converted into biologically active messengers or mediators, and because they have 22 carbon atoms we suggested calling them docosanoids.

We began looking at them intensively in various conditions linked to the function and diseases of the eye and of the brain, and in 2003 and 2004 we participated in the discovery of Neuroprotectin D1, which is the first messenger or mediator of DHA. We characterised this molecule and found that sure enough it's involved in experimental ischemic stroke, and it's involved in functions, and these functions of the eye and of the brain included Alzheimer's disease.

As I understand it, DHA and docosanoids, its derivatives including Neuroprotectin D1, are there to help protect neurones. Is that correct? Can you tell me more about this?
In our laboratory, we design 'hypothesis-driven' experiments. So, we have ideas and we test them. The science must be driven by rigour, and the rigour of science is how you design experiments and how you test a hypothesis. During this process, although we always have ideas, we have a lot of surprises, a lot of unexpected findings. And although we predicted that there were going to be docosanoids, our findings were more surprising and had other implications than those we had predicted.

It must have been a very exciting time to be working in the laboratory.
It still is, because this is an ongoing exploration. In fact, now we have a set of new molecules that we will be reporting in the near future, that we have recently discovered in my laboratory and that could actually be an additional game changer in understanding all of these responses.

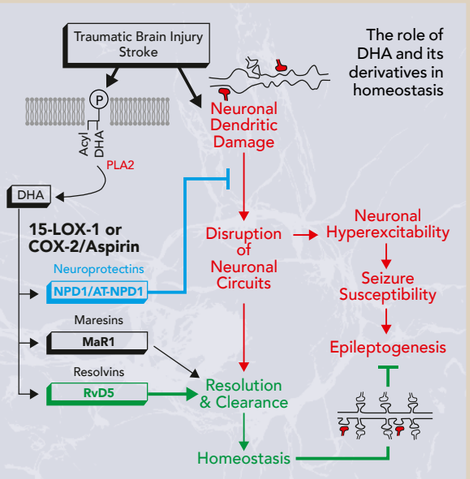
We wanted to decipher how the brain or the retina responds very early on to injury or to the onset of pathology. Just think for example about Alzheimer's disease. If we go into a model of Alzheimer's or into a donor patient's brain with Alzheimer's disease and try to see the changes happening when the disease is already fully on-board, it's very difficult to identify the causality. What are the early events? Over many years, my laboratory has focused almost exclusively on very early events of several models of diseases. All these diseases that we are talking about have no cure, but we believe that if we can decipher what happens very early in them, we might be able to harness those events to create disease-modifying therapies.

So how close do you think we are to a treatment for a condition like Alzheimer's or Parkinson's?
That is a very important question. I believe we are much closer now than five or ten years ago. We have much more information. We have many more experimental approaches, and we have new clues about the early disease development through the work of many people throughout the world. We also successfully applied NPD1 and these concepts in cellular models that recapitulate aspects of Parkinson's disease. I believe that, if we can slow down the onset or early disease progression in the next few years it will be a tremendous triumph, because Alzheimer's disease is very complex and it's multifactorial, and it has many aspects that make it a major threat to humanity nowadays.

Absolutely, and as our worldwide population ages, it's becoming more and more prevalent, isn't it?
Yes, because age is the number one risk factor and one woman out of five over the age of 65, no matter what we do in the next few years, will get Alzheimer's disease. Also one man out of eleven over 65 will get Alzheimer's. We do not know why there's this difference, that's one of the clues that nature gave us, and we are actively exploring the gender difference.

The magnitude of this disease is tremendous, for the care givers, for the families and for the health care system. This is something that will have a growing and tremendous impact on humanity in the near future.

It's very interesting also that the second cause, what I would call the number one environmental cause of Alzheimer's disease is traumatic brain injury, and we are neglecting this. Trauma to the brain is an environmental risk factor for cognitive dysfunctions like Alzheimer's disease.



The role of DHA and its derivatives in homeostasis

Some of the clinician–scientists who work closely with Dr Bazan: (from left) Rostyslav Semikov, MD, MSc; Hemant Menghani, MD; Ifeanyi Iwuchukwu, MD; Janet Rossi, MD

That's really interesting, isn't it? It certainly suggests an area to look into.
Well these things give us hints in order to go and design experiments where we can actually go into the intimacy of the molecular principles that are involved in the development of diseases like these. Many laboratories now are using a stem cells-like approach as well. In my laboratory, we are reprogramming adult cells into induced pluripotent stem cells (iPSCs) that become neurones, enabling us to get an insight into molecular principles of neuronal survival and neurorestoration. Then, having those cells in the laboratory, one can identify which are the molecular mechanisms that are actually changing, and also one can use those cells to test experimental compounds that could become drugs or treatments in the future. So the development of having neurones differentiated from patient-specific iPSCs can recapitulate molecular phenotypes of Alzheimer's disease or other neurodegenerations. This human genomics approach will also facilitate implementation of precision medicine.

To go back to your question, "When can we have a treatment?" the answer is, there are enough tools and information that make me very optimistic that we are going to see at least effective treatments to slow down onset and early disease progression in the not too distant future.

Which is fantastic news, isn't it? It's amazing that things are progressing like that. As a global population we are getting a lot older. Do you feel that ageing and age-related diseases are getting enough priority and focus at the moment?
I believe so. I want to take this opportunity to tell you that ageing is not a disease. Many people will age successfully. Successful ageing means, like many people that you and I know in their 80s or 90s, having cognition and sight preserved. We have many examples throughout history, Albert Einstein, for example.

Ageing doesn't mean disease, and I think that's one of the challenges of neuroscience. We need to find what is it that could make us age successfully. We know certain things: we know, for example, about certain dietary recommendations. We know also about physical activity and intellectual activity, and there are genetic predispositions, and epigenetic changes that we don't understand very well. So, during ageing a multitude of factors converge that lead us to think about the brain and sustaining cognition, and about the retina and preserving sight, because these functions use very important cells.

When you first started looking at the relationship between DHA and the retina you were using the eyes as a way to find out more about the brain, and then you started discovering a lot of really interesting things about the eye itself. Is that right?
Absolutely. This was Argentina in the early 70s and we didn't have many resources. We would go at three in the morning to the slaughterhouse, get cows' eyes as they processed the meat, bring them to the laboratory and peel the retinas off. And that was a beautiful nature-made brain slice. We began by asking questions that we were interested in because of the neurological and ophthalmological implications. And suddenly it became very apparent that diseases of the retina, like age-related neurodegenerative diseases, for example Alzheimer's, and other diseases of the brain have mechanisms in common. The retina is an exceptional model to ask questions of the brain, but it's also a very important organ that fails in ageing and many vision-related diseases, some inherited, some age-related.

One aspect that fascinated me very early on about the retina, was the cell called the retinal pigment epithelial (RPE) cell which can eat the tip of the photoreceptors every day in our eyes. Thus necessity, due to lack of funding in the early 70s, made us design experiments using toads that became ideal to ask these retina questions.

This is a fascinating process.
Yes, it is very fascinating. It's called phagocytosis and, every day, the tip of each photoreceptor is shed and is phagocytosed by this cell. The RPE cell then processes the remains of the photoreceptor and retrieves certain molecules back to the retina to rebuild part of the photoreceptor cell daily. This is called renewal of the photoreceptors and among those molecules that are retrieved is DHA. So we identified those processes, and named the loop that brings DHA back from the cell to the retina, the short loop (the one that brings DHA from the diet, truly from the liver, to the retina and brain, we named the long loop several years ago) and we've been trying to understand how this process is regulated because the retinal pigment epithelial cell is the most active phagocyte in our body. We have many, many cells in the body that do phagocytosis and the function of them is different to the one in the eye.

That is something that fascinated me from the very beginning, because phagocytes throughout the body are there for eliminating dead cells, eliminating debris, eliminating foreign bodies, but these RPE cells eat the tip of the photoreceptor by phagocytosis in order to renew that structure, that photoreceptor cell that is obviously essential for vision.

Yes, and with the long loop DHA is sent from the liver up into the brain. Does that mean that your diet can affect the amount of DHA that's in your brain? So, if you eat a diet rich in fatty acids that could help increase the levels in your brain?
The answer is yes. However, we found in my laboratory here in New Orleans in the 80s that DHA and its precursors need to go through the liver before going to the brain and to the retina. So even today we don't understand how it is that the brain and the retina tell the liver, 'Send me DHA' when they need it to build or regenerate membranes. So, despite a good diet with good amounts of omega-3 fatty acids like DHA, it's important to realise there might be impediments to the delivery by the liver. In fact, about six years ago it was reported that in inherited forms of Alzheimer's patients there is a deficit in liver enzymes for DHA metabolism.

How do you find the time for it all?
Perhaps it's that you have a motivation and a vocation of service. I feel that I'm in a quest to find, as I said earlier in this beautiful chaos, to find a molecular logic. How is it that biology has come up with the extraordinary cells that we have in our retina and in our brain? How can we put these things together in biology and then move into medicine, and eventually be able to help people with diseases when that logic fails? And so it's easy. It's just an easy task and that motivation is a driver in my mind in a way. It's there seven days a week, 24 hours a day and it's very spontaneous.

It's very inspiring to hear about everything that are achieving and have achieved. Are there any things that you're particularly proud of?
Well, we have five children and I'm very proud of them. Each of them has their own successes and their own activities, and so that's something that I'm very proud of. And now they have given us 12 grandchildren and two additional step grandchildren. Of course, my wife, also a scientist, has been fundamental to everything that we have talked about today. And I'm very proud to have a lot of colleagues in different stages of their scientific life working with me. So, those are very important components of my life.

Dr Bazan celebrates rather than laments the difficulties he has faced, saying 'adversities bring strength and renewed perspective'

All photography by Daryl Schmitt

Detail

RESEARCH OBJECTIVES
Dr Bazan's work focuses on uncovering the molecular processes that underpin neurodegenerative diseases such as Alzheimer's and Parkinson's, age-related macular degeneration, traumatic brain injury, pain, epilepsy and stroke. Much of his current work centres on deciphering the molecular principles of mitochondria significance in cell survival, autophagy, neuroinflammation and single cell transcriptomics that underlie neuroprotective and neurorestorative activities of DHA and its derivatives, including novel approaches to neural stem cell generation and applications.

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COLLABORATORS
Nicos Petasis (USC, CA); Julio Alvarez Builla Gomez (U. Alcala, Spain); Dennis Rice (Novartis, Cambridge, MA); Jennifer Lentz, Ludmila Belayev and Walter Lukiw (LSU, New Orleans); Ricardo Palacios Pelaez (Diater Lab, Spain); Andy Obenaus (LLU, CA); Marianne Schulzberg (KI, Sweden); Charles N Serhan (Harvard, MA)

BIO
Dr Bazan is the founding Director of the Neuroscience Center of Excellence at the Louisiana State University Health Sciences Center, School of Medicine, New Orleans. He has been appointed to the highest academic rank in the LSU System, a Boyd Professor (1994-present) and is also: the inaugural founder of The Ernest C. and Yvette C. Villere Chair for Research in Retinal Degeneration (1984-present); a Founding Senate Member of the German Center for Neurodegenerative Diseases (DZNE) 2009-2016; Foreign Adjunct Professor of Neuroscience in the Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Sweden (2016-); Chairman Emeritus of the Board of Governors of the Association for Research in Vision and Ophthalmology (ARVO) Foundation.