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David Rubinsztein: Autophagy and neurodegeneration

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Professor David Rubinsztein stands as a pioneering force in neurodegeneration research, revolutionizing our understanding of autophagy's critical role in combating diseases like Huntington's, Parkinson's, and Alzheimer's. This exclusive Genomic Press Interview reveals the journey of the Cambridge-based scientist whose groundbreaking discovery that autophagy regulates the clearance of toxic aggregate-prone proteins has transformed therapeutic approaches to neurodegenerative diseases worldwide. As Professor of Molecular Neurogenetics at the University of Cambridge and UK Dementia Research Institute Group Leader, Rubinsztein has authored over 400 scientific papers and ranks among the world's most highly cited researchers, with over 134,000 citations demonstrating his extraordinary impact. His laboratory's pioneering work identifying autophagy upregulation as a therapeutic strategy has opened unprecedented avenues for drug development, earning him exceptional recognition, as exemplified by Fellowship of the Academy of Medical Sciences, EMBO membership, and Fellowship of the Royal Society. His transformative contributions have been honoured with prestigious awards, including the Roger de Spoelberch Prize, the Thudichum Medal, and the Movement Disorders Research Award from the American Academy of Neurology, alongside consistent recognition as a Clarivate Analytics Highly Cited Researcher. Beyond his scientific achievements, this intimate portrait reveals Rubinsztein's dedication to mentoring the next generation of scientists, his passion for classical music, and his philosophy of pursuing curiosity-driven research. From his early days in Cape Town to becoming the first UK-trained genetic pathologist, his remarkable career exemplifies how fundamental discoveries in cellular biology can translate into hope for millions affected by neurodegenerative diseases, positioning autophagy modulation at the forefront of therapeutic innovation.

Figure 1. David C. Rubinsztein, MB ChB, BSc(Hons), PhD, FRCPath, FMedSci, FRS, University of Cambridge, United Kingdom.

Part 1: David C Rubinsztein – Life and Career

Where were you born, and where do you live now?

I was born in Cape Town, South Africa, and now live in Cambridge, United Kingdom.

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

My parents were not scientists or physicians. However, my father loved puzzles and was curious about science. He subscribed to Scientific American and was particularly interested in mathematics and logic. I grew up in an environment where it was natural for me to read lay scientific books and magazines, and I enjoyed the challenge of solving problems. I was particularly interested in mathematics and biology at school and was fascinated by genetics. I studied medicine at university and was influenced by the personal tragedy that is associated with childhood genetic diseases, when I did a project early in my studies, which involved interviews with parents of a child who had died from Tay-Sachs disease.

After completing my medical degree and housejobs, I decided to gain some research experience. The head of the department I wanted to work in, Prof. Wieland Gevers, suggested that I (and others who had studied medicine) first do a year-long BSc(Hons) degree to fill in some of the gaps in my scientific education before starting a PhD. This was a crucial step for me, as I learned a lot of key scientific concepts, how to read papers, and gained some experimental experience. I then pursued a PhD where I identified mutations in the LDL receptor in South Africans of Indian origin and characterised their cell biology. I was fortunate to have excellent mentors – Denys van der Westhuyzen and Gerry Coetzee. Their lab had an outstanding scientific environment, and they taught me

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about the value of curiosity and the importance of robust experimentation and analysis. After my PhD, I decided to pursue a career as a physician-scientist focusing on genetics. I went to Cambridge, where Prof. Malcolm Ferguson-Smith recruited me. I was the first UK trainee in "Genetic Pathology" – a new arm of laboratory medicine that had just been created to develop medical doctors with skills in genetic diagnosis. This was a forward-looking idea in the early 1990s. I was fortunate to have Prof. Ferguson-Smith and his successor, Prof. Martin Bobrow, as supportive and encouraging mentors, who helped me develop my research during this specialty training.

Soon after arriving in Cambridge, the Huntington's disease gene was published. I started working on the population genetics of the gene and other microsatellites. However, I then reached a stage where I wanted to understand more about how the mutation caused disease and pivoted my efforts to develop cell, Drosophila, and zebrafish models of the disease. It was clear from early on that the mutation was mediating its effects through a gain-of-function mechanism. Initially, inspired by the work of people like Ulrich Hartl, we worked a bit on chaperone proteins and other aspects of proteostasis in the disease. But after learning what autophagy was, we decided to test if this clearance pathway was relevant for mutant huntingtin clearance. Our initial experiments using chemical tools that could induce or compromise autophagy in mammalian cells showed that autophagy could clear mutant huntingtin. Importantly, we demonstrated that boosting autophagy could reduce the levels of the disease-causing protein and ameliorate its toxic effects. We then went on to show that autophagy regulates the clearance of other neurodegenerative disease-causing proteins like tau (in Alzheimer's and other dementias) and alpha-synuclein (in Parkinson's). Our subsequent studies in zebrafish and mice have shown that autophagy is a crucial clearance pathway for these proteins and that one can ameliorate their deleterious consequences in vivo by boosting autophagosome formation. This has set the scene for most of our subsequent work studying the effects of these proteins on autophagy, developing therapeutic strategies for these diseases based on autophagy upregulation, and understanding signalling and mechanistic aspects of autophagosome formation.

Please share with us what initially piqued your interest in your favourite research or professional focus area.

The consensus in the field was that mutant huntingtin caused disease via a toxic gain-of-function mechanism. Thus, a logical approach is to find ways of reducing the level of the toxic mutant protein. The ubiquitin-proteasome system was a possibility but was limited because the narrow entrance of the proteasome could not accommodate oligomeric protein species that are seen in many neurodegenerative diseases. I became aware of the potential of autophagy after reading a paper by a colleague, Aviva Tolkovsky, who was studying autophagy in cell death contexts. I was struck that autophagy could clear large structures like ribosomes and mitochondria and thought that this may be a way that cells could use to clear oligomeric proteins or small aggregates in the cytoplasm, as one has in Huntington's disease, Alzheimer's disease, and Parkinson's disease.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channelled you toward that leadership responsibility?

I have had leadership roles as the Academic Lead of the Alzheimer's Research UK (Alborada) Drug Discovery Institute in Cambridge and as Deputy Director of the Cambridge Institute for Medical Research. I held the former position for 7 years and the latter for about 13 years (although I will soon be coming to the end of my term). I was asked to take these roles by the senior leadership. I am not sure there were defining moments.

What is a decision or choice that seemed like a mistake at the time but ended up being valuable or transformative for your career or life?

I am having trouble coming up with anything that fits this. One should make decisions and then make the best of the choice one has made and not look back. One cannot conduct a controlled trial to assess whether the alternative not pursued would have been better or worse.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

In the early phases of my career as a group leader, I received two very useful pieces of advice from more experienced colleagues. The first was to focus one's research efforts and not become too diffuse. The second was to identify the strengths in each postdoc or student and direct their activities towards those strengths.

I strongly believe in being in the lab to be available for discussions and advice, where I can help. My office has always been in the lab.

I have always tried to cultivate a friendly, supportive, and collaborative laboratory atmosphere. I want my students and postdocs to be excited about coming to work, like I am.

My PhD mentors emphasised the importance of journal clubs both as vehicles for keeping up with the literature and for teaching. I have always had a weekly journal club in my lab where we discuss one paper in depth for about 45 minutes. I keep in touch with both the specific literature pertinent to the projects we are working on, as well as more general developments. I make a habit of scanning the index pages of *Nature*, *Science*, *Cell*, *Molecular Cell*, *Neuron*, etc, to spot interesting developments outside our direct lab activities.

Please tell us more about your current scholarly focal points within your chosen field of science.

We are trying to understand:

1. Mechanisms of autophagy dysfunction in neurodegenerative diseases
2. Ways we can enhance cellular protein clearance for treating neurodegenerative diseases
3. How autophagosomes are shaped by cells and the regulation of autophagosome biogenesis.
4. Cellular consequences of autophagy compromise.
5. Non-autophagic roles of autophagy proteins.

What impact do you hope to achieve in your field by focusing on specific research topics?

We hope this will help the understanding of the pathobiology of neurodegenerative disease and contribute to therapeutic development.

What do you most enjoy in your capacity as an academic or research leader?

Seeing new results, discussing what they mean, and developing strategies to address the questions that new data present.

At Genomic Press, we prioritize fostering research endeavours based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that you feel strongly devoted to?

As scientists, we have the privilege of interacting with colleagues from different countries and cultures. It is essential to foster these links to learn both scientifically and culturally, and to break down some of the existing barriers.

As group leaders, we have a responsibility to train the next generation of basic and clinical scientists. I am proud that trainees from my lab have been successful in academia and industry, both in the UK and in many countries abroad.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

I love classical music – I spend much of my leisure time listening to music or playing the cello or piano (see Figure 2).

Figure 2. David Rubinsztein playing his cello, which he describes as his "most treasured possession." Music is an important part of his life outside the laboratory.

Part 2: David C Rubinsztein – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?
Enthusiasm.

Among your talents, which one(s) give(s) you a competitive edge?
Ability to prioritise, delegate, and trust.

If you could change one thing about yourself, what would it be?
Keep some of my controversial views to myself a bit more.

What is your current state of mind?
Grateful for the good things in my life.

What is your idea of perfect happiness?
I do not think there is "perfect happiness". But I am happiest when people around me and I are happy.

When and where were you happiest? And why were so happy then?
I do not have such extremes of happiness or sadness. My moods are relatively stable. However, I was recently thrilled and moved when my twin daughters graduated from their different medical schools.

What is your greatest fear?
Something bad happening to my family.

What is your greatest regret?
My parents and siblings live in Sydney, while I have lived in the UK, so we have not seen each other as much as I would have liked for more than 30 years.

What are you most proud of?
My children, my students, and my postdocs.

What do you consider your greatest achievement?
Our discovery reveals that autophagy plays a crucial role in clearing aggregate-prone proteins, which cause diseases such as Huntington's disease, tauopathies, and alpha-synucleinopathies/Parkinson's. Furthermore, we have found that boosting autophagosome formation can ameliorate the toxicities of these proteins in both cell and animal models.

What or who is your greatest passion?
My wife, Judy.

What is your favourite occupation (or activity)?
Lab meetings discussing results.

What is your greatest extravagance?
High-quality cello strings.

What is your most treasured possession?
My cello.

Where would you most like to live?
I am happy living in Cambridge, UK.

What is the quality you most admire in people?
Common sense.

What is the trait you most dislike in people?
Virtue signalling.

What do you consider the most overrated virtue?
Athletic ability.

What do you most value in your friends?
Honesty.

Which living person do you most admire?
Joseph Goldstein and Michael Brown. They did transformative work in physiology and cell biology on lipid metabolism that provided important clinical insights and impact. I studied many of their key papers when I was younger and was inspired by their scientific brilliance and determination to get to the bottom of key problems.

Who are your heroes in real life?
Pablo Casals and Mstislav Rostropovich – two great cellists and musicians. While both revolutionised cello playing in their generations and led to the instrument becoming an important solo vehicle, they are my heroes for their humanism as advocates against fascism/Franco (Casals) and Stalinism (Rostropovich), and their courage opposing totalitarian regimes.

[1] In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for $130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

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If you could have dinner with any historical figure, who would it be and why?
Bertrand Russell – I read his autobiography when I was younger, and this made a big impression. I suspect he would be an excellent conversationalist with fascinating views pertinent to today's challenges.

Who are your favourite writers?
Charles Dickens – I read many of his novels as a child and was often moved by the plots and the social issues that he highlighted.

Jan Swafford – a brilliant biographer who has written excellent books on Mozart, Beethoven, and Brahms, which capture the personalities and lives of the composers and their musical achievements, while placing them in the contexts of the philosophies and political movements of their times.

Who are your heroes of fiction?
Pip (Great Expectations).

What aphorism or motto best encapsulates your life philosophy?
My school and University motto – Let us be judged by our deeds.[2]

[2]The motto "Let us be judged by our deeds" (Latin: *Spectemur Agendo*) is the motto of the South African College Schools (SACS) in Cape Town, South Africa. This includes both SACS Junior School and SACS High School. SACS is the oldest high school in South Africa, having been founded in 1829, and is well-known for its strong values-based ethos and long-standing traditions.

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