

Questions and Answers with Dr. Juan Pascual

Highlights:

- A view into operations of a world-class medical research program at UT Southwestern
- New C7 studies beginning 2014 from the team that developed C7 for G1D
- Patients may participate whether or not they are on a ketogenic diet
- Insights on developing treatments for rare disorders
- C7 as a dietary supplement
- The bigger picture: the future of human and laboratory research in G1D

Can you tell us more about your lab environment at UT Southwestern? Our laboratory is a central part of a vibrant top research, teaching and medical care institution with about 100 buildings, nearly 2,500 hospital beds on campus and 5 Nobel Prize laureates—more than any other medical school in the world, and who are instrumental to our work in the lab. We welcome students, visitors and colleagues from all over the world.



The core staff of the lab includes four faculty members--myself as the principal investigator, two senior research scientists, two advanced postdoctoral researchers, one senior researcher and an advanced technician, together with several levels of administrative support (<http://goo.gl/o16gPU>). We routinely work with other UT Southwestern labs on topics of mutual interest, given the highly collaborative environment and diverse expertise within UT Southwestern. We also collaborate with other labs within

and outside the greater University of Texas System. In our lab, projects are shared and vigorously discussed--formally on a weekly basis and informally just about any time during the day. Lab members are free to pursue independent inquiries and establish their own research programs. This is already happening and gives me great satisfaction. A research laboratory is only as good as each one of the researchers that are part of it, and although we routinely receive inquiries from extremely qualified scientists who wish to join us, I believe that we have achieved the optimum balance with our current staff. Of course, we also benefit substantially from the separate clinical personnel and operations under the umbrella of the university hospital, for which I am very grateful. UT Southwestern is unusual in that it owns most of its own hospitals, enabling the research and patient care aspects to be more interrelated than at other institutions.

How is your research funded? We are salaried employees of the State of Texas, including faculty with clinical duties such as myself. That is, our salary is not connected with patient care activities, and we are not sponsored or supported by any private financial interests. As a result, we are free to pursue any and all scientific and medical research that we consider most appropriate for our patients. We consider the pursuit of an

academic research career as a vocation. Most support comes from the NIH as peer-reviewed, competitive grant awards; other significant funding comes from the Glut1 Deficiency Foundation, private donors and my endowed professorship (<http://goo.gl/y55jQk>). I, as principal investigator, am ultimately responsible for generating funds to cover salaries and lab expenses. I spend a great deal of time writing grant applications and looking for sources of funding. Generally, only the NIH is capable of funding a significant, 5-year project. However, we employ smaller grants and donations of any size very effectively to hire key personnel or advancing new work on high-impact ideas that later allow us to apply for much larger grants.

What is the lab working on at this time? To my knowledge, our program is unique in that we tackle medical problems at multiple levels, starting from the molecules that make up the brain, to the neurons that are altered as the result of mutations or metabolic alterations, to the conduct of clinical trials--all while providing front-line clinical consultation and care for many patients afflicted by the very disorders that we are investigating in the lab (G1D being a prime example). We have an extensive track record of original, peer-reviewed publications, matched with highly competitive research funds from the National Institutes of Health (NIH). Our range of expertise is broad, and I am never sure whether the next invitation to collaborate with another lab or to lecture at another medical school will focus on molecules, cells, animal models of human disorders, medical aspects of certain disorders, clinical trials or the ethics of human research and treatment methods. I welcome them all, because each of these aspects is essential to comprehending the complete picture and, over the years, I have become convinced that no single approach will solve the problems that we tackle in the lab. That is why the expertise of our lab staff is so diverse, and why we engage with so many outstanding colleagues world-wide. I firmly believe that the primary role of a University professor is to teach others so that they learn from our successes and errors as they develop their own approaches, and hope that our experiences will help reveal the path to future advances by the next generation. Our sophisticated and novel tools and techniques are already revealing aspects of brain function in general and G1D in particular that were unknown before. These discoveries are opening doors to other areas for research and, ultimately, better treatments. In my mind, this is why our work as a whole is so important, and why our approach and methods transcend particular results, such as a new finding in a G1D mouse brain or analysis of the results of one particular clinical trial.

Among a variety of recent initiatives, we conducted an initial, extremely fruitful study of triheptanoin (also known as C7) as a treatment for Glut1 deficiency (G1D) during 2012 – 2013. Our study was facilitated in that C7 is an affordable triglyceride oil, with a long-standing safety record supported by its common use in food and other consumer applications such as cosmetics, as well as by Dr. Charles Roe's extensive work with C7 to treat patients with other metabolic diseases. Based on our initial study results, we are currently planning an additional series of studies related to C7 and G1D. In enabling this important research, we are grateful for a \$25,000 donation from a patient family, the long-standing work and vision of Dr. Charles Roe from the lab, enthusiastic assistance from the Glut1 Deficiency Foundation and other patient families, and the unmatched support of UT Southwestern.



In answer to questions that I routinely receive, I would like to note several points:

- There are several manufacturers of C7, and it is available to researchers qualified to receive FDA approval for their investigations.
- We have made a number of widely disseminated 'public disclosures' about the potential of C7 in G1D, starting in 2010 at our annual G1D Foundation conference and culminating with our 2012 article in the Journal of Cerebral Blood Flow and Metabolism (Nature Publishing Group: <http://www.nature.com/jcbfm/journal/v33/n2/full/jcbfm2012151a.html>).
- I feel strongly that there should be no intellectual property or any other restrictive proprietary interest (belonging to us or anyone else) in the use of C7 to treat G1D that could impact the availability of C7 for G1D research. I emphasize that C7 (let alone the use of C7 in G1D) is not the idea or invention of any brokerage, lobbying or drug company, and so I believe, from an ethical standpoint, that research with C7 should proceed independently of any commercial, profit-seeking effort.
- I envision C7 (if and when conclusively determined beneficial as a dietary supplement to help treat G1D) following the same route as MCT (medium chain triglyceride) oil to become broadly and economically available to patients. C7 is an edible oil derived from castor beans, much like MCT, which usually is derived from coconut oil (but which contains mainly C8); see additional details here: <http://goo.gl/e8rkSO>). There is no secret; C7 is deceptively simple to make in this day and age, as compared with most other medical foods, drugs and other substances that I have used in my career.
- In my view, which I share with all the patients I know, it is not in the interest of G1D patients for anyone 1) to seek "drug-designation" status for C7 (as there is no known case in which this has not impacted treatment costs and required agreement by insurance companies for reimbursement), 2) to try to restrict the distribution of C7 for the purpose of limiting medical research to those investigators who agree to cooperate with a commercial effort to obtain a drug

designation for C7; or 3) to lobby for rapid approval shortcuts, which could allow commercial exploitation of C7 without adequate research into its effects on G1D. I believe that rare diseases deserve no less due process from the FDA and from researchers than any other disease. They ought to be at least as well understood as any other disease before we start treatment—rare disease patients are no more tolerant to trial and error than any other patient, and, as we know, “trial” and “error” form a couple. Shortcuts are likely to undermine confidence and credibility (see: <http://www.ncbi.nlm.nih.gov/pubmed/22992075>). Moreover, confidence and credibility are secondary when compared with the risks of premature use of a substance for patient treatment. We will not accelerate any treatment at the risk of a patient’s wellbeing given how little we know about G1D. I do not understand why some still are able to consider rare diseases a territory where treatment standards can or should be relaxed, streamlined or accelerated, when our knowledge of human biology is still drastically incomplete – as illustrated by profound gaps in our understanding and treatment not only of rare diseases, but also of common diseases (i.e., Parkinson’s disease, Alzheimer’s disease, multiple sclerosis, most cancers, epilepsy, diabetes, coronary artery disease, stroke, rheumatic and joint diseases, etc.).

- No commercial effort to profit from C7 will impact our research in any way—for the sake of patients, I believe that this is an ethical boundary that should be acknowledged and not crossed. Whether C7 oil (or an array of related and unrelated therapies that we are also developing) will work fully, or partially, just for some, or not at all, my lab’s research must continue unbiased in the best interest of all G1D patients until we and our peers are fully satisfied with the evidence that we produce. Of course, no financial interests, consultancy payments, confidentiality agreements, right to publication clauses, data ownership contracts, or any other commercial schemes or motivations do or will play any role in the outcomes or data that our lab will be analyzing and reporting (regardless of the practice at so many other places). Fortunately, the same principles apply to many others across the world with whom our team closely communicates and collaborates. This is the core of a vigorous debate on the ethics of commercial sponsorship of medical research, which continues to grow as patients become more informed.
- Another major initiative that has gathered significant attention and gained us extremely valuable collaborators is The Glucose Transporter Type I deficiency syndrome Research Consortium (G1DRC) (<http://goo.gl/CdV0YA>).
- Other research areas we are pursuing are described on our website (<http://goo.gl/o16gPU>).

When are the next C7 studies going to start? We are awaiting some final steps in the approval and funding process, which we are confident, will enable us to pursue all aspects of the planned research, including brain metabolism analysis by MRI, simultaneous EEG and functional MRI, and comprehensive testing of additional metabolic interventions. Our unique study design is comprehensive--almost 200-pages long--and is currently undergoing advanced-level review. I am already receiving almost daily requests for enrollment! Please bear with us and with our regulatory institutions. 2014 promises to be a very exciting and busy year for the G1D community.

What type of patients will participate in these studies? The majority of G1D patients, whether or not on a ketogenic diet will be eligible, until a certain maximum number are enrolled. In our previous C7 study in G1D we found that measurements of brain metabolism and other assessment tools are so reliable that there is no need for a placebo or another C7 substitute. At the conclusion of the new studies, patients should be able to continue to take C7 if they request (after institutional review and approval), as was the case following the past C7 study.

When do you expect them to be completed and the results shared? We always try to be extremely efficient. Last year we diagnosed and followed a large number of G1D patients, published a record number of peer-reviewed articles and book chapters and presented our work at many professional conferences. I spent much time typing inside aircraft and hotel rooms! The publication date for the past C7 investigation will depend on the complexity of the studies we carry out and on the findings we come across along the way. For example, because all ages--ranging from very young children to adults--were included, and because brain metabolism was directly assessed (using MRI), the analysis becomes very complex. Metabolism (including brain metabolism) changes throughout life, such that one study becomes several parallel studies and vast quantities of data are generated and must be analyzed. We are keenly aware of the importance of the data and our analysis to all G1D patients, and are working diligently to communicate our results by peer-review publication. Our academic advancement, future funding and intellectual reputation depend on the quality and usefulness of what we publish. NIH is now evaluating researchers on the basis of how promptly they publish their studies and how effective their data sharing procedures are. In our typical grant proposal to the NIH, we include a detailed data-sharing plan and are evaluated (and eventually funded) to a large extent on the basis of this plan. We more than welcome these recent developments.

What potential does this research have to impact the big picture of Glut1 Deficiency (and perhaps even more conditions)? If C7, as an example, could replace or even just improve the efficacy or tolerability of the ketogenic diet, we will have taken a major step forward in the treatment of G1D. It is notable that our investigations are taking place as we approach the 100th anniversary of the first ketogenic diet work. The longevity of this single technique illustrates how complex our research field is, and also highlights how new methods that we have developed are enabling us to generate radically novel ideas. I believe that more importantly than the development of any single therapy, we are shedding new light on ages-old scientific and medical questions for the benefit of those who are ill. If you asked me or any lab member whether there could be a higher satisfaction in life, the answer would be a resounding "no." That satisfaction comes from having seen a live brain cell function very differently from the way we were taught, from finding new principles that describe how brain circuits develop and communicate, and from holding a child that has improved after treatment. In my view, and as the history of medicine shows, prestige, financial gain or power are not compatible with the pursuit of knowledge for the benefit of all. No important, ground-breaking discovery has ever been brokered by a board of directors or revealed through the vision of a lobbyist. X-rays, penicillin, anesthesia and MRI are examples of this. We deceive ourselves if we think otherwise.

How does this project reflect your overall approach to research and medicine? What principles guide these new studies?

Principles guide moral decisions. With regard to C7, my view, which is in line with most experts who care for patients and understand G1D, is that C7 should be offered (if and when appropriate) as a dietary supplement and not as a drug. There are also 'grassroots' patient initiatives that are very sensitized to the issues surrounding the cost and availability of new treatments, and these initiatives are gathering momentum. How C7 may ultimately be made available to patients will not be finally determined by us, but by patients and their elected representatives. A regulatory designation for C7 will determine both accessibility and cost. We provide the science in experimental animals, the molecular mechanisms, much of the safety data, human studies, etc., but we also care for our patients as human beings. We do not see any reason why a product already used in the food industry should be re-presented or re-priced as a drug, with all that that implies for availability, as long as proper regulatory procedures remain in place. What about those among us who are much less fortunate than we are, or who live in poor countries? If the benefit of C7 is established, the case should be argued as to why C7 should be treated any differently from the very similar MCT oil. We use food-grade C7 oil, which has been the subject of extensive testing in other human metabolic diseases by Dr. Charles Roe, and also has been used in the European dairy industry as well as other human applications in our country. We have been very pleased so far with the initial safety and outcomes of our G1D patients taking food-grade C7, and have found no chemical, biological or medical (let alone ethical) justification for a drug-designation approach. If making C7 more broadly available is advanced as a justification, then let us see an analysis of the ultimate cost to patients, profit margins and evidence that insurance will be willing to reimburse for C7. I would also like to know how poor families would obtain it. Excessive cost limits us in the clinic on a daily basis from using even some common medications and other medical care that otherwise would greatly benefit our patients.



From a broader perspective, I believe that the G1D questions that we initially laid out are solvable, that we can make a difference in solving them and that we must stand clear of any suspect financial gain--because we are career scientists, and our mission is our vocation. We will always try to do what we promise. Where we find previous knowledge is outdated, incomplete, useless or simply wrong, we will develop new ways to rectify it. Others may believe that knowledge is already sufficient -- that what we need are better brokers or lobbyists, that it is all a matter of putting the pieces together, and that, as in the corporate world, success is a matter of economics. We simply cannot understand why this should apply to medical science and patient care, notwithstanding its prevalence in the culture we live in today. Every person is endowed with sufficient sense to see the truth, but also with the power to ignore or distort it, which is a uniquely human capacity. Robert Louis Stevenson wrote that even an ant or a tiger knows that there are things that they should not do.

What can the G1D community do to be helpful and where can we find more information?

Foremost, please register at www.G1DRegistry.org as soon as possible with whatever information you have or can recall. At a minimum, knowing the number of patients will be very helpful so that we can plan and advocate for more and better research for the benefit of all. The registry is confidential, unrelated to any drug or lobbying firm, and can accept as little or as much information as you may have available.

More information about our current clinical studies (periodically updated) is available at <http://goo.gl/IUITID>

An updated publication record from our lab and clinic can also be found here <http://goo.gl/j1UaPD>

Thank you very much for the opportunity to provide this update and for your immense support. Feel free to write to me at Rare.Diseases@UTSouthwestern.edu.

A handwritten signature in black ink, enclosed within a thin black rectangular border. The signature is cursive and appears to read "Dennis".

These reflections are of a personal nature and do not necessarily reflect the views of UT Southwestern Medical Center, The Glut1 Deficiency Foundation or any other person or organization