

Q&A with Gino Cortopassi:

How long have you been involved in FA research and what got you interested in FA?

I started working with Franco Taroni on FA lymphoblasts and fibroblasts in 1997, and we published our first paper on FA in 1999, showing that the FA patient cells were more sensitive to oxidative stress.

What led you to become interested in DMF as a potential therapy for FA?

We had a talented student who had been in pharma for 10 years, who came to my lab in 2009, Sunil Sahdeo. I started him screening drugs for FA, and he identified DMF as a potential candidate in January 2011. Later that year we received a Kyle Bryant award from FARA and characterized the hits from the screen (DMF and two others).



I think the money for the Kyle Bryant award in 2011 came from RideAtaxia events like the one held 1 June 2019 in Winters, CA, that I rode in with an especially inspiring Ataxian, shown at left. Kyle came to my office at UC Davis shortly after having been diagnosed with FA, about 2005. Instead of isolating himself he eventually founded RideAtaxia which generated the funding to test DMF's efficacy in laboratory animals. And that has led to new therapeutic mechanisms and a FARA-sponsored clinical trial as described below.

Legend. Kyle and Gino after Norcal Ataxia bike ride, June 1, 2019.

What are the key findings in this paper, and what does it tell us about FA that we did not know previously? Why is this particularly exciting?

Two things are particularly important in this study. One is that work from Francesco Sacca's lab that shows that multiple sclerosis patients treated with DMF have increased frataxin as measured in blood cells. This shows that DMF is increasing mitochondrial protein expression in humans. Mittal Jasoliya showed in 2017 that Friedreich's patients, frataxin-deficient mice and cells from FA patients all have a defect in mitochondrial number and gene expression. So reversing that with DMF could be important for the disease. Hayashi and Jasoliya showed that DMF dose-dependently increases frataxin expression and mitochondrial number in a different publication.

The second reason that this is exciting is that DMF 'removed the brakes' put on frataxin gene expression due to the GAA repeats and the R-loops. So, this paper confirms that there are more 'transcriptional pauses' that the RNA polymerase experiences in the frataxin gene as a consequence of the GAA repeats. So the RNA polymerase 'train' is slowing down in its reading of frataxin as the result of the GAA-repeats, and that only at these GAA repeats there are R-loops. What the paper clearly shows is that DMF 'releases the brakes', increasing frataxin gene initiation, and reducing the time the RNA polymerase pauses at the pause sites, and less R-loops as well. Our interpretation is that the DMF causes more initiations at the frataxin RNA start site, which causes the RNA polymerase train to drive more often or more forcefully through the RNA 'pausing sites', so they still slow the train down, but the end result is more frataxin expression.

Should FA patients take DMF?

FA patients should not start taking DMF yet as its efficacy has not been proven in humans with FA, but we hope to know soon if it is effective. Dr. Sacca is starting a clinical trial to test if DMF is effective in FA in Italy, and we hope this will tell us if the drug works. The whole reason for us to initiate a screen of drugs that were already approved for other diseases in 2009 was that all 1600 drugs we screened had a known safety profile. So DMF has a known safety profile. And that is one of the reasons that the regulatory authorities could approve its use in a clinical trial relatively quickly, because it already has been dosed in >200,000 people with multiple sclerosis and >3000 people with psoriasis. This will help FDA and EMA to more rapidly approve DMF for FA, if the current clinical trial's results are good.

What are the next steps in this research? What do we hope to learn?

We are still trying to learn how DMF increases frataxin in particular and mitochondrial proteins in general. We are also trying to determine the optimal dosing for the most profound pharmacodynamic effect. We have found that frataxin genes of normal C57Bl6 mice respond in a dose dependent way to DMF, in the range of 100-160mg/kg, and we are about to start testing these doses in FA mouse models.