Rapamycin, mTOR, TNF Inhibition, RA, Longevity and Canadian Content: Putting the Puzzle Pieces Together

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Why do most continuing medical education (CME) presentations start with a patient case? Because science is more interesting when you can relate basic research to clinical innovations which will help your patient. This journey started with a message to call a patient of mine, a man with long-standing rheumatoid arthritis (RA) well-controlled on conventional disease-modifying antirheumatic drugs (DMARDs), as he wanted to discuss a new therapy he had read about online. What that therapy was, he wouldn't confide to my secretary.

It was a quiet day, so I returned his call. What could he have found? I was guessing cannabinoids, turmeric, noni juice, apple cider vinegar, bee venom or the like. No, he was interested in rapamycin (sirolimus). I told him I was familiar with it as an immunosuppressant and anti-rejection drug, but it was not approved for RA therapy. I did promise I would look into it further and let him know more at his next appointment.

I figured rapamycin might have been investigated in the past and failed in RA. True and false. A quick search found a EULAR (European Alliance of Associations for Rheumatology) abstract poster from 2018 reporting such a study (FRI 0063): "Rapamycin induces remission in patients with refractory rheumatoid arthritis" by H. Yao and colleagues.[1] Fifty RA patients treated with DMARDs for more than 6 months who did not achieve DAS-28 (Disease Activity Score in 28 joints) remission were enrolled and treated with rapamycin at a dose of 0.5 mg every 2 days for 24 weeks. Rapamycin treatment reduced RA disease activity and induced DAS-28 remission in 44.9% of active RA patients. Of course, there was no placebo group. I haven't seen anything since on the topic, other than an abstract on a similar study at the American College of Rheumatology (ACR) 2018 meeting.[2]

Other than reporting this back to the patient as promised, I thought that was the end of the matter. However, a few days later I received a financial news email I subscribe to from John Mauldin, a prolific and interesting writer. While he is generally gloomy on the financial future, he is very optimistic on advances in health care and biotechnology, particularly regarding extending the human lifespan. Not only was he discussing rapamycin, but also tumour necrosis factor (TNF) inhibition. The word for that is serendipity.

Dr. Erwin Gelfand and Dr. Philip Baer in Antarctica, in 2019.

Mr. Mauldin reported on a company called MyMD Pharmaceuticals[3] which he had invested in (MYMD on NASDAQ, if you want to take a flyer and are prepared to potentially lose your entire investment). "Their drug, MYMD-1 is a TNF-inhibitor. . . Unlike monoclonal anti-TNF antibodies, MYMD-1 is an orally administered synthesized version of a naturally occurring molecule found in plants." The company website indicates a molecular weight of 146 Daltons, the ability to cross the blood-brain barrier, and that "MYMD-1 selectively blocks TNF when it becomes overactivated in autoimmune diseases and cytokine storms, but does not block it from doing its normal job of being a first responder to any routine type of moderate infection." All very interesting if it pans out, but the drug is just now entering Phase 2, which many drugs do not survive.

Is the company studying their drug for RA? Not directly. Their trial is targeted to aging and specifically to reversing sarcopenia, which is of course a feature of uncontrolled RA. And that's where rapamycin comes in. Rapamycin is the gold-standard treatment for countering aging and increasing lifespan in mice. MYMD-1 markedly outperformed rapamycin in a mouse longevity study (in press apparently) performed by scientists at Johns Hopkins.[4]

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If you look online, you will find a lot of articles about off-label anti-aging therapies, with metformin and rapamycin most often touted. You can skip those, but I highly recommend a review by Dr. Daniel Sabatini, one of the leaders in research on rapamycin and its target mTOR.[5]

What will you learn? "Dr. Sabatini chose to investigate the molecular mechanism of rapamycin, a compound with antifungal, antitumour, and immunosuppressant properties. The decision was pivotal because Sabatini went on to discover the mechanistic target of rapamycin (mTOR) protein and signalling pathway, which serves as a central regulator of cell metabolism, growth, and proliferation."[6] Interesting naming to begin with: just like Lou Gehrig died of Lou Gehrig's disease, rapamycin's target mTOR happens to be named after rapamycin.

The mTOR protein turns out to be a central player in many cellular processes. "mTOR is the major regulator of growth in animals and is the key link between the availability of nutrients in the environment and the control of most anabolic and catabolic processes. Signalling of mTOR is deregulated in common diseases, like cancer and epilepsy, and mTORC1 (a complex containing mTOR) is a well-validated modulator of aging in multiple model organisms. There is significant excitement around using mTORC1 inhibitors to treat cancer and neurological disease and, potentially, to improve healthspan and lifespan." As Dr. Sabatini states, he never believed "the mTOR pathway would receive the recognition it has and eventually even be derided for 'doing everything'."

To bring this all home, the review figures show some of the molecules which interact with mTOR. These include some suggesting Canadian roots, such as RAPTOR (nothing to do with basketball; it is the Regulatory Associated Protein of mTOR) and CASTOR (our national symbol the beaver is Castor canadensis, but this is the Cytosolic Arginine Sensor for mTORC1). But rather than stretching for Canadian-themed content, Dr. Sabatini provides a real link, referencing research on rapamycin by Dr. Erwin Gelfand, a prolific immunologist, and a McGill graduate who was formerly on staff at the Hospital for Sick Children in Toronto. As you can see in the photo on page 3, I met Dr. Gelfand for the first time in Antarctica in 2019. Let me assure you, we did not spend our time talking about rapamycin.

Rapamycin for RA may be a dead end, but if my patient hadn't called me about it, I would never have learned any of the above!

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