MacularNEWS

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New Study Reveals Why MacTel Strikes the Macula – and How We Might Stop It

What Is the Macula and Why Is It So Important?

The macula is a small but mighty part of the retina at the back of our eye. It is responsible for our sharp, detailed central vision – the kind you need for reading fine print, driving or recognizing faces. Because the macula works so hard to give us clear sight, it can also be more prone to wear and tear. This hardworking patch of tissue is often the first place to show damage in many eye conditions.

A Disease Focused on the Macula

Most people have heard of age-related macular degeneration, another form of macular degeneration is Macular Telangiectasia Type 2, commonly known as MacTel. This is a less common, progressive eye disease that may cause gradual loss of central vision, often in both eyes. MacTel never spreads beyond the macula so it only ever affects central vision, never peripheral vision. Patients might not notice it at first, but over time they may find reading or seeing fine detail becomes difficult. Under the microscope, one of the hallmarks of MacTel is the loss of certain support cells in the retina called **Müller cells**. These Müller cells act like the retina's caretakers and scaffolding – they nourish other cells, keep the environment healthy and provide structural support. Müller cells in the macula start to disappear in MacTel, which causes degeneration of the photoreceptors, the cells that detect light. The question is: Why do these vital support cells die off, and why only in the macula? What makes this area for central vision so vulnerable?

Director's Message

In this issue of **MacularNEWS**, we highlight our laboratory's Macula-on-a-Chip findings that explain why MacTel affects the macula and shows that re-balancing macular chemistry may help slow or even prevent vision loss.

Thank you for your continued interest in our work. I hope you enjoy reading this issue.

Professor Mark Gillies
Macula Research Group

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Clues from Chemistry – A Toxic Imbalance

Recent research has uncovered an important clue. It turns out that patients with MacTel have a subtle chemical imbalance: they have unusually low levels of an amino acid called **serine** in their bodies. Serine (along with a partner amino acid called **alanine**) is one of the building blocks cells use to make proteins and fats. When everything is in balance, cells use both serine and alanine in harmony. But if serine runs low, cells are forced to use more alanine – and this can lead to trouble. Specifically, the cell may start producing **deoxy-sphingolipids**, or **DeoxySLs** – which are essentially *toxic fat-like molecules*. Think of it as a recipe gone wrong: with the right amount of ingredients (enough serine), everything is fine, but take some of it away and the cell ends up cooking up a toxic byproduct. These DeoxySLs were found to build-up in the eyes of people with MacTel, and scientists suspected that they might be poisoning the retina's support cells. This was a strong hint that MacTel could be driven by a chemical mishap in the macula – but why the macula specifically?

The Macula's Unique Metabolism

Researchers in our Macular Research Group set out to answer that question. The big challenge was that you can't study a human macula easily in a living person, and laboratory animals like mice don't even have a macula. The solution was an innovative system we call the "**Macula-on-a-Chip**." In this system, tiny pieces of donated human macula tissue are kept alive in a special chamber – essentially a mini life-support unit for the retina. The tissue is bathed in nutrients and oxygen, allowing it to stay healthy for at least five days. In those crucial days, we can safely test what happens to real human macula cells under different conditions, something not possible with traditional animal models. This means we can mimic aspects of MacTel, and macular degeneration in general, in a dish and observe the results, almost like watching the disease unfold in real time – all thanks to the generosity of eye donors who provided the retinal tissue.

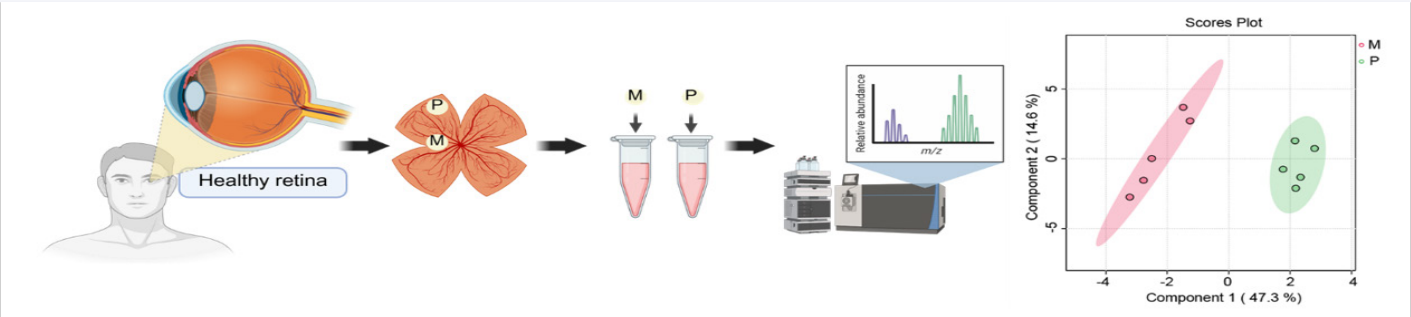


Figure 1: Studying How Fats Work in the Human Macula

*Using the MoaC system, we profiled the composition of the retina's fats and discovered that even healthy maculas (**M**) have significantly more DeoxySLs than the peripheral retina (**P**). The pink dots show that the macula has a distinct fats composition compared to peripheral retina (green dots).*

Using the Macula-on-a-Chip, our scientists made a fascinating discovery about how the macula handles nutrients. Even in normal (healthy) donated eye tissue, the macula behaves differently than the peripheral parts of the retina. It was found that the macula naturally produces more alanine and makes less serine relative to alanine than other regions of the retina. In other words, the **serine-to-alanine ratio** is naturally lower in the macula. Why is this important? This imbalance – more alanine and less serine – means the macula is sitting close to a metabolic "tipping point." Under normal circumstances, this balance might not cause harm. But if serine levels drop even a little (as they do in MacTel patients), the macula is primed to start overproducing those toxic fat-like molecules, DeoxySLs.

Our study of the fats in the human retina (**Figure 1**) confirmed that the macula tissue had distinct fats profile and accumulated significantly more DeoxySLs than the peripheral retina. This helps explain a long-standing mystery: **why MacTel strikes the macula first**. The macula's unique chemistry makes it the most vulnerable spot – it's the part of the retina most likely to tip over into a toxic state when key nutrients are out of balance.

Recreating Mactel In the Lab

Showing a chemical imbalance is one thing, but the team also wanted direct evidence that these toxic molecules were the actual culprits harming the retina. To do this, they recreated MacTel-like conditions in the Macula-on-a-Chip. Researchers introduced a surge of DeoxySLs (the toxic molecules) to healthy human macula tissue in the chamber, essentially simulating what might happen in a MacTel-affected eye. The result was striking: the retina's cells began to suffer damage, and tellingly, the cells that were hardest hit were the Müller cells – those crucial support cells that we know disappear in MacTel. Under the microscope, the treated tissue showed signs that Müller cells were dying off, almost as if the scaffolding of the retina was starting to collapse. This was the smoking gun the scientists were looking for. It demonstrated that **DeoxySLs directly cause harm to the macula's support cells**, kick-starting the disease process seen in MacTel. In a sense, the team watched MacTel happen in a dish – proving that the toxic imbalance can actively drive the damage.

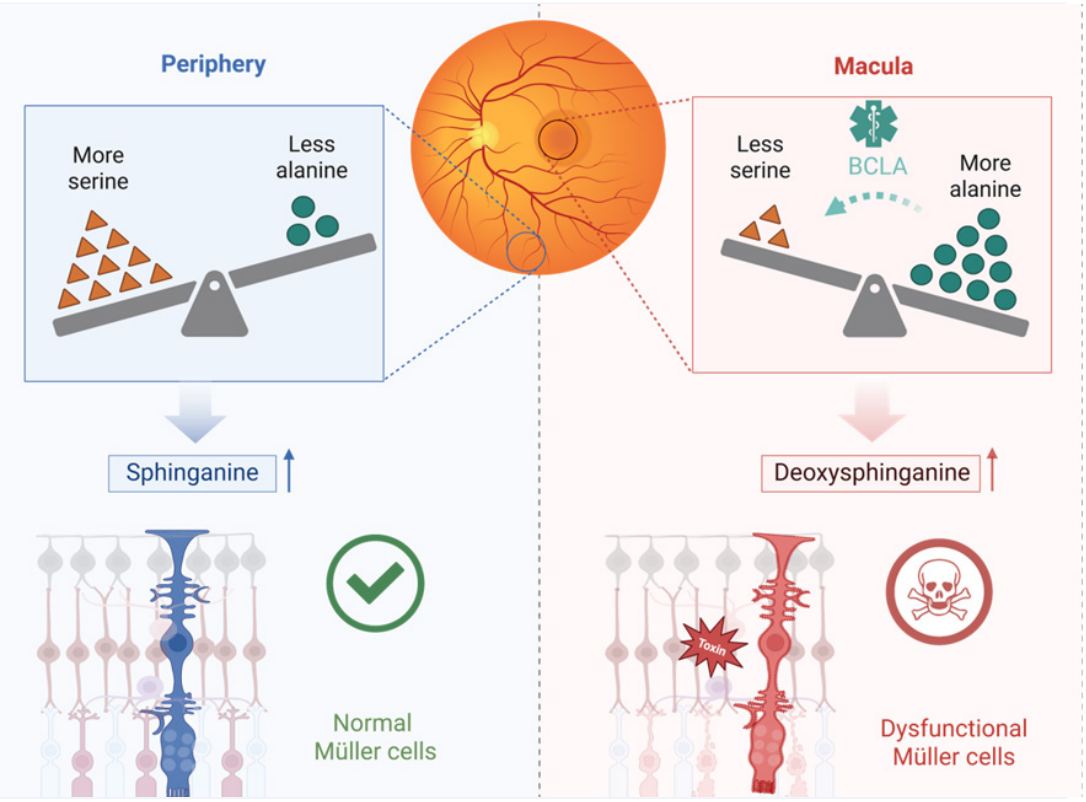
A Potential Way To Protect the Macula

Armed with this new understanding, the researchers immediately asked the next critical question: ***Can we stop it?*** If the overproduction of alanine (and the resulting toxins) is injuring the macula, perhaps reducing alanine or restoring the balance could protect the eye. The team focused on an enzyme called **ALT (alanine transaminase)** – essentially the cell's machinery for making alanine. They discovered that ALT is highly active in the macula's Müller cells, meaning these support cells are a key source of the excess alanine. Thus, the idea was to temporarily block ALT and see if that spared the retina. In the lab, they added a compound called **β-chloro-L-alanine (BCLA)** to the Macula-on-a-Chip system. BCLA's job is to inhibit ALT – think of it as putting the brakes on alanine production. The outcome was very encouraging: with ALT slowed down, the macula tissue's alanine levels dropped and the serine-to-alanine balance shifted back toward normal. Consequently, the production of toxic DeoxySL molecules fell significantly. Most importantly, the retinal cells – including the vulnerable Müller support cells – stayed healthier under this condition. In short, by rebalancing the retina's chemistry, the team **prevented the usual damage** from occurring.

Hope for the Future (Figure 2)

This breakthrough study has shed light on the chain of events that makes the macula so susceptible in MacTel. We now understand that the macula's own metabolic makeup puts it at risk when nutrients are out of balance, leading to toxic molecules that can destroy support cells. The exciting news is that we also see a way to intervene early. If we can find safe methods to adjust the retina's chemical balance – whether through a new drug, a dietary supplement like extra serine, or some other intervention- we may be able to slow or even halt the progression of MacTel. While more research is needed before this approach can be turned into a treatment for patients, the path is clearer than ever. By pinpointing a root cause of macular damage in MacTel, scientists have opened the door to therapies that protect the macula before vision is lost, rather than just trying to manage symptoms. It's a hopeful step forward for everyone affected by this disease. And thanks to innovative tools like the Macula-on-a-Chip – and the generous donors who make such research possible – we are entering a new era of understanding macular diseases, one where prevention and preservation of sight become tangible goals.

Figure 2: The Root of MacTel and a Path to Protect Vision



Through our Macula-on-a-Chip work, we have learned why the macula is especially vulnerable in MacTel. We found that its metabolism is different — it naturally makes more alanine and less serine. When serine drops, this imbalance leads to toxic molecules, DeoxySLs. These toxins build up more in the macula than anywhere else and damage Müller cells — the retina's key support cells. We also found that Müller cells are producing this extra alanine, through an enzyme called ALT. By blocking ALT, we were able to restore the chemical balance, reduce toxic buildup, and help protect the retina. This gives us a new way of thinking about macular disease — not just watching damage happen, but finding ways to prevent it, starting at the molecular level.

If you would like to make a tax-deductible donation or discuss leaving a bequest to support macular research please visit our website **sydney.edu.au/medicine/eye**, call us on **(02) 9382 7309** or post a cheque to: Save Sight Institute, South Block, Sydney Eye Hospital, 8 Macquarie Street Sydney NSW 2000 made out to 'The University of Sydney'

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