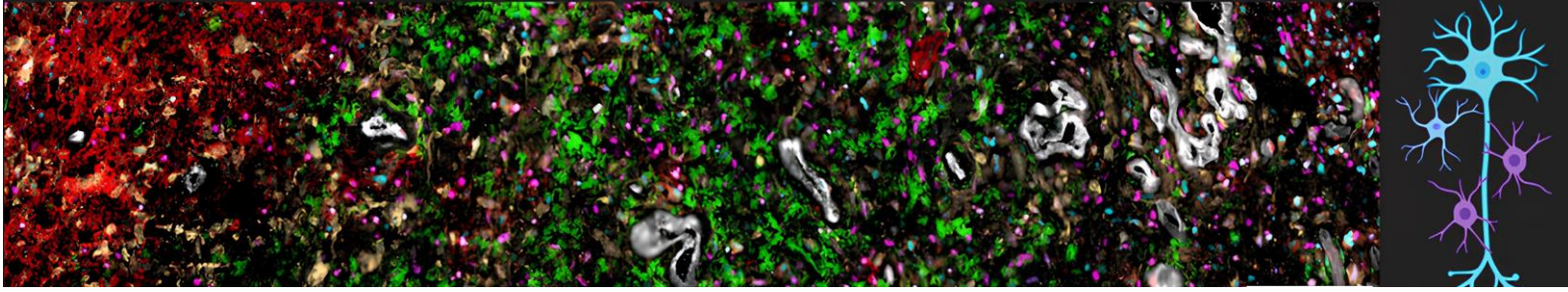

Does glioblastoma have a floor plan?

The oxygen gradient behind the architecture

Written by Njabulo Dlomo, Hons | 03.08.2026

When a neurosurgeon resects a brain tumour, they are operating around a boundary that they cannot actually see. They remove the visible tumour and a margin of the normal-looking brain tissue around it. Yet, in 90–95% of recurrent cases, the tumour returns within 2 cm of the primary site (De Bonis et al., 2013).

In part, it is because glioblastoma (GBM) is an aggressive brain cancer with a short survival period of about 15 months (Grochans et al., 2022), and it is heterogeneous: a single tumour can contain cells that are in completely different states. Most of what we know about those states comes from single-cell RNA sequencing, which works by breaking the tissue apart into a suspension of individual cells. You learn which states exist. Yet, you lose where they were — which cells sat next to the blood vessels, which sat beside immune cells, and which sat at the edge, up against the healthy brain.

In 2024, a team led by researchers at the Weizmann Institute of Science and Massachusetts General Hospital (Greenwald et al., 2024) asked something that sounds almost too simple for a tumour this lethal: **does glioblastoma have a floor plan?**

Reading the tissue without taking it apart

They laid tumour slices onto slides printed with a grid of barcoded spots, so every reading came with an address attached. Across patients, the same fourteen programmes kept reappearing. Eight are states cancer cells slip into rather than fixed identities; the other six belong to the normal cells caught up in the tumour — macrophages, blood vessels, neurons. Then they asked whether those states sit together or scatter. The answer was that it depends entirely on where in the tumour you look. Some regions are organised, others are chaotic, and every tumour contains both.

Oxygen is what decides which is which

The state that clustered most reliably was the one the team called MES-Hyp (**mesenchymal-like hypoxia-related** tumour cells): cancer cells in the oxygen-starved zone around the dying tissue.

On its own, this was unremarkable: hypoxic cells sitting together is exactly what hypoxia looks like. What was remarkable was what happened to everything else around them. Every other cancer cell state sat more neatly arranged when it was near the hypoxic zone than the same state did in regions with no hypoxia at all. This meant that the structure was never the hypoxic patch itself. It was the way that everything else arranged itself around it.

They checked this against neurons, which cluster for reasons that have nothing to do with oxygen. Neurons clustered just as tightly, but the tissue around them was never as structured.

So, hypoxia is not marking the organised regions. It is organising them into five layers, running from the oxygen-deprived core outward to the brain the tumour is invading (**Figure 1**).

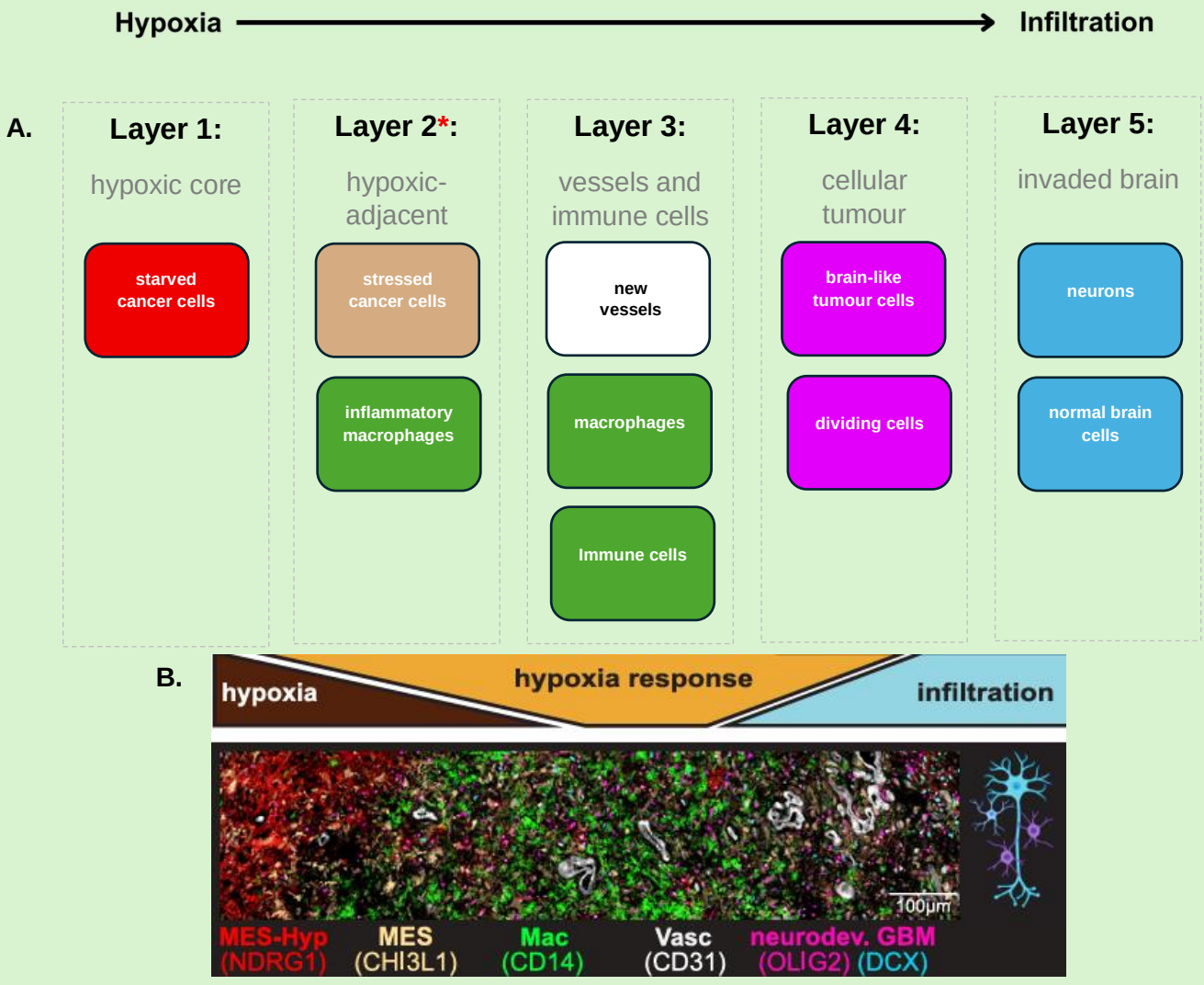

Figure 1: **The five-layer architecture of glioblastoma. (A)** The cell states occupying each layer, running from the oxygen-starved core (L1) out to the invaded brain (L5). **(B)** The same ordering in the paper's own staining: starved cancer cells (red) give way to macrophages (green), blood vessels (white), and finally brain-like tumour cells (magenta). The whole gradient, core to margin, spans about a millimetre. Panel A adapted and panel B reproduced from Greenwald et al. (2024), *Cell*, under CC BY 4.0.

* The layer no microscope has ever named.

What this changes

Four of those five layers already have names. L1 is pseudopalisading necrosis, L3 is microvascular proliferation, L4 is the cellular tumour, and L5 is the leading edge. Pathologists have been describing them down a microscope for decades.

However, **L2 has no histological equivalent**. It is the ring of hypoxia-adjacent states sitting just outside the suffocating core — invisible on a stained slide, and only there when you look at cell state instead of cell shape. The organised tissue detected molecularly was also far more extensive than the organised tissue a pathologist can see — the structure runs further out than the eye can follow. Out towards the margin, which is exactly where the tumour comes back.

I want to be careful not to oversell this. Hypoxia was inferred from the MES-Hyp state rather than measured directly, and the attempt to prove causality failed: GBM organoids dropped to low oxygen switched on hypoxia markers but never produced the layered structure — probably because an organoid has no vessels, no immune cells, and no real gradient to respond to. Hypoxia-as-organiser is strongly supported but is yet to be proven.

Still, it reframes the disease. I had been carrying around an image of glioblastoma as rogue cells running uncontrollably. This paper suggests something closer to a badly built tissue that still follows rules — driven by suffocation but organised. And I think that rules are something you can eventually draw a floor plan from.

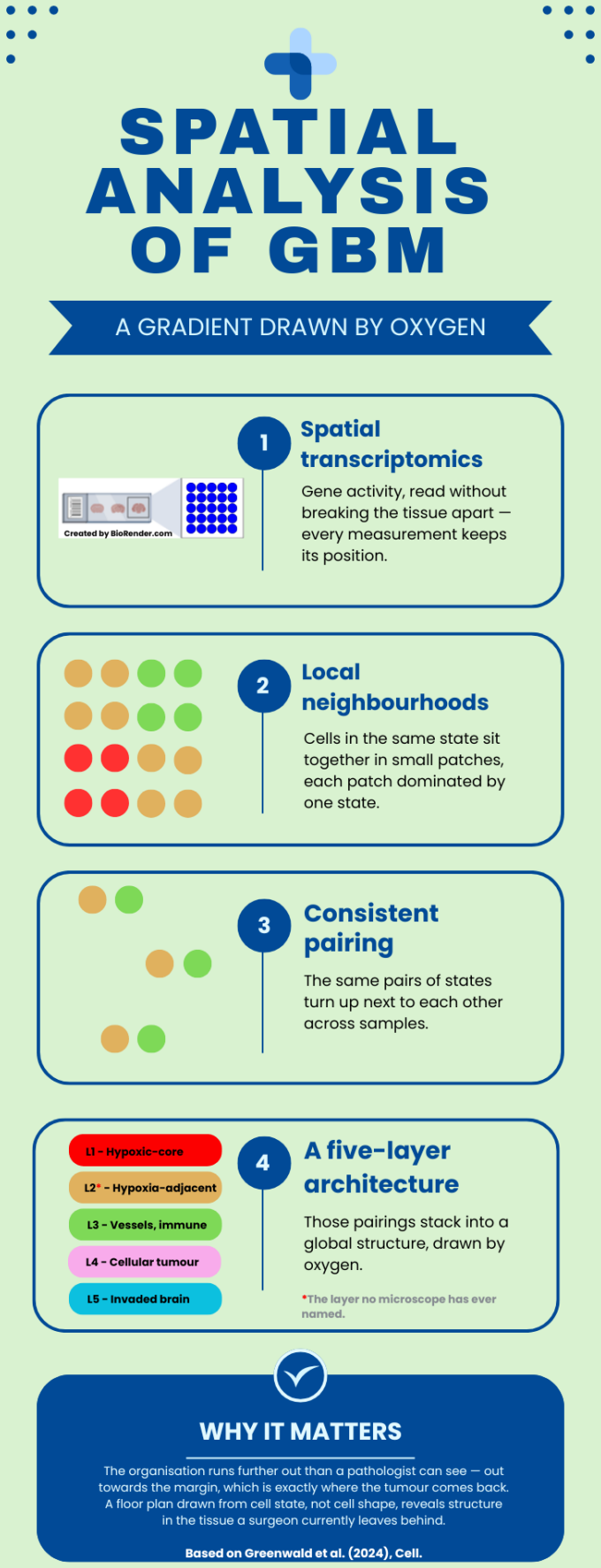

Figure 2: How the five-layer architecture was found. From tissue read in place, to local patches of a single state, to the pairings that stack into a gradient drawn by oxygen. Based on Greenwald et al. (2024), *Cell*.

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