

Review Article

$\gamma\delta$ T Cells and the Extracellular Matrix: From Established Adhesion to an Unmapped Mechanotransduction Pathway in Barrier Immunity, Neuroinflammation and Cancer

Abiha Baig¹¹. University of Leicester, United Kingdom

$\gamma\delta$ T cells are disproportionately enriched in the ECM-rich barrier tissues of the gut and skin, and are already known to adhere to the extracellular matrix (ECM) through a broad integrin repertoire, including CD103, CD49a and the wider $\beta 1$, $\beta 2$ and $\beta 7$ integrin families. In conventional $\alpha\beta$ T cells, this kind of integrin-ECM engagement has been shown to drive a defined intracellular mechanotransduction pathway: actin polymerisation, nuclear deformation and YAP translocation that together promote IL-2-dependent activation, independently of the T cell receptor. Whether the same pathway operates in $\gamma\delta$ T cells has never been tested, even as recent work shows that $\gamma\delta$ T cells respond functionally to matrix viscoelasticity. This review brings together the descriptive literature on $\gamma\delta$ T cell behaviour at barrier tissues with the mechanistic mechanotransduction literature built in $\alpha\beta$ T cells, to argue that the molecular link between the two, rather than ECM engagement in general, is the genuine and clinically relevant gap. It distinguishes this ECM-mechanosensing question from TCR mechanosensing, considers a possible bidirectional feedback loop between $\gamma\delta$ T cells and the matrix they occupy, and develops testable, disease-specific hypotheses in inflammatory bowel disease, chronic wound healing, traumatic brain injury and multiple sclerosis, and solid tumour immunotherapy, each linked to an existing drug or clinical precedent.

Correspondence: papers@team.qeios.com — Qeios will forward to the authors

Introduction

The extracellular matrix (ECM) is essential not only for providing structural support but also for conveying information to cells. Stoker and colleagues first demonstrated this in 1968, showing that cell adhesion to a rigid surface is necessary to complete mitosis. This finding established that the ECM does not merely support replication, but also directs growth, differentiation, and apoptosis. As cells attach to the ECM, they form focal adhesions, the junctions that link the cytoskeleton to the extracellular space. These links are central to mechanotransduction, the process by which physical and mechanical signals are converted into biochemical signals that direct cellular behaviour.

This raises a significant question: given that tissue stiffness varies enormously, from soft tissues such as brain and lung to rigid bone, how do cells calibrate their response to match the specific mechanical demands of their local environment? This calibration depends on a balance between two signalling directions: outside-in signalling, in which the ECM directs cell behaviour, and inside-out signalling, in which cells actively remodel the ECM around them. Both directions rely on functioning mechanotransduction to remain in balance. When this bidirectional signalling is disrupted by ageing or disease, ECM turnover becomes dysregulated, with pathological consequences. In cancer, tumour cells signal to fibroblasts to stiffen the surrounding stroma, a process that promotes invasion. In cardiac injury, a similar loss of balance drives fibroblasts to overproduce ECM, resulting in cardiac fibrosis^[1].

The ECM is understood today as a dynamic, physiologically active part of the immune landscape, not an inert scaffold. It is made up of fibrillar proteins such as collagen and fibronectin, glycosaminoglycans, proteoglycans, and mucus, and together these create a microenvironment that shapes immune cell behaviour. The ECM physically guides where immune cells move and where they sit, and heparan sulfate proteoglycans within tissues bind and present chemokines, forming the directional gradients that leukocytes follow. ECM composition and stiffness are also sensed through dedicated mechanosensing machinery, including mechanosensitive ion channels such as Piezo1, so the matrix regulates immune cell survival, mobility and function through the same kind of bidirectional signalling described above for cells in general^[2]. Almost all of this mechanistic work on how ECM stiffness and composition are converted into an intracellular signal has been done in conventional $\alpha\beta$ T cells, macrophages and stromal cells. This is not to say $\gamma\delta$ T cells are unstudied in relation to the ECM: they are already known to adhere to it through a broad integrin repertoire, spanning $\beta 1$, $\beta 2$ and $\beta 7$ family integrins, and this adhesion has been linked to their tissue retention, migration and effector function across several subsets^[3]. What has not

been established is whether that adhesion is read out through a defined intracellular mechanotransduction pathway, of the kind now mapped in conventional $\alpha\beta$ T cells, or whether it operates only through the simpler adhesive and migratory roles already described. This paper reviews what is known about $\gamma\delta$ T cell biology and their documented physical relationships with the ECM, and argues that, despite an established and growing literature on $\gamma\delta$ T cell-ECM adhesion, the specific molecular pathway by which that adhesion might be converted into an intracellular signal remains unmapped.

$\gamma\delta$ T cells were first identified in 1984, distinguished from conventional $\alpha\beta$ T cells by their use of γ and δ chains instead of α and β chains in the T cell receptor. $\alpha\beta$ T cells recognise peptide antigens only in the presence of major histocompatibility complex (MHC) molecules, whereas $\gamma\delta$ T cells can recognise antigens independently of MHC, including stress-induced molecules and non-peptide antigens that $\alpha\beta$ T cells cannot detect. This structural difference plays a major role in shaping their distinct functions. Activation mechanisms also differ: $\gamma\delta$ T cells can be activated by a single signal, while $\alpha\beta$ T cells require two signals, antigen recognition plus co-stimulation. This equips $\gamma\delta$ T cells with features of both innate and adaptive immunity, allowing them to respond faster and without prior antigen exposure^[4].

$\gamma\delta$ T cells make up only about 1–5% of circulating T cells in peripheral blood but are present at much higher proportions in specific tissues, reaching nearly 40% of intraepithelial lymphocytes in the intestine and 10–30% of T cells in the skin. Alongside this tissue enrichment, $\gamma\delta$ T cells are actively involved in tissue surveillance at barrier sites, contributing to tissue homeostasis^[4]. This tissue distribution is worth pausing on, because it places $\gamma\delta$ T cells exactly where the ECM is most abundant, most mechanically varied, and most often remodelled by injury and infection. That is what makes the absence of any dedicated account of $\gamma\delta$ T cell ECM sensing so noticeable.

This tissue enrichment is not spread evenly across one uniform $\gamma\delta$ population, but reflects a small number of subsets defined by which γ - and δ -chain variable regions they use. In human peripheral blood, the dominant subset is V γ 9V δ 2, which recognises phosphoantigens independently of MHC and is the subset most commonly used in current cellular immunotherapy programmes. V δ 1 cells, by contrast, are rare in blood but dominate the tissue-resident compartment described above, in the gut, skin and other epithelial barriers^[4]. In mice, the equivalent tissue-resident populations are organised by γ -chain usage and by the developmental wave in which they seed a given tissue: the epidermis is populated almost exclusively by a single invariant subset, discussed further below, while the gut and other tissues are populated by more heterogeneous waves of $\gamma\delta$ T cells. This subset structure matters for the rest of this review, because it means that any ECM-sensing mechanism, if one exists, would not necessarily be

uniform across the $\gamma\delta$ lineage. A tissue-resident subset such as V δ 1, which stays anchored to an ECM-rich niche long-term, seems a more plausible candidate for a dedicated mechanotransduction pathway than a circulating subset such as V γ 9V δ 2, which only meets the ECM briefly.

$\gamma\delta$ T cells and the extracellular matrix: adhesion, mechanics and a missing mechanism

Both $\alpha\beta$ and $\gamma\delta$ T cells depend on integrin-mediated adhesion to move through tissue barriers, but the two lineages have not been studied to the same depth when it comes to what these integrins actually do once they grip the matrix. T cell interactions with the ECM happen through integrin family adhesion receptors, which connect the intracellular actin cytoskeleton to ECM components such as fibronectin, laminin and collagen. Gray and colleagues studied human $\gamma\delta$ T cells across a range of tissues and found that tissue-resident $\gamma\delta$ T cells, specifically the V δ 1 subset, express two surface integrins, CD103 and CD49a, which bind E-cadherin and collagen respectively. Expression of these proteins is higher in the gut and increases with age^[5]. This finding matters for two reasons. It confirms that $\gamma\delta$ T cells are not just sitting inside ECM-rich tissue, but are physically gripping the matrix and its adhesion molecules using the same integrin toolkit as other tissue-resident lymphocytes. But it also stops at the level of description: the study identifies the receptors without asking whether engaging them triggers any of the intracellular signalling that has been mapped in such detail for $\alpha\beta$ T cells. That open question runs through the rest of this review.

Gray and colleagues' CD103/CD49a finding should be read as one entry in a considerably larger literature, not as the first evidence that $\gamma\delta$ T cells engage the ECM at all. Siegers' review of integrin biology in $\gamma\delta$ T cells catalogues a much broader repertoire: β 1, β 2 and β 7 family integrins have each been implicated in $\gamma\delta$ T cell adhesion, tissue retention, transendothelial migration and, in several settings, effector function, across multiple $\gamma\delta$ subsets and tissues, not only the V δ 1/CD103/CD49a axis emphasised above^[3]. Set against that literature, describing $\gamma\delta$ T cell-ECM engagement as unmapped would overstate the gap: what integrin-dependent adhesion does for $\gamma\delta$ T cells, in terms of where they go and how long they stay, is already reasonably well established. The open question this review is concerned with sits one level down from that, at the point where ECM engagement is converted into an intracellular signal beyond the adhesive event itself.

The wider immunology literature makes clear that this is not a small thing to leave unanswered. Sutherland, Dyer and Allen's review of ECM-immune biology shows that the ECM is not simply a physical barrier, but actively shapes how T cells move through tissue. T cells prefer to travel through regions with thin, loosely organised collagen and fibronectin fibres, and avoid dense matrices that have been stiffened by cross-linking enzymes such as lysyl oxidase (LOX). This is an active process: the mechanical properties of ECM fibres, including how much they can stretch, directly regulate integrin binding and the signals that follow from it. Inflamed skin is a clear example of this, where structural changes to fibronectin fibres strengthen integrin binding to the point of stopping T cell migration altogether, so that cells build up at perivascular sites instead of moving deeper into the tissue. This kind of mechanosensing is not limited to integrins either; mechanosensitive ion channels such as Piezo1 show that immune cells can respond to physical force more broadly, and TGF- β together with type 2 cytokines such as interleukin-13 have their own role in changing how much ECM is made and what it is made of. Taken together, this shows that ECM mechanics do not just restrict where T cells go, but actively shape their behaviour through integrin-mediated mechanotransduction^[2]. Every one of these findings comes from mixed T cell populations or from conventional $\alpha\beta$ T cells. None of it has been tested in $\gamma\delta$ T cells on their own, even though $\gamma\delta$ T cells are the resident lymphocyte at exactly the tissues, skin and gut, that these studies use as their models.

Work in $\alpha\beta$ T cells has since gone further and worked out a specific integrin-mediated mechanotransduction pathway at the molecular level. Feng and colleagues showed that when $\alpha\beta$ T cells engage a stiff ECM through their integrins, F-actin polymerises and bundles up near the cell surface where the integrins are gripping the matrix. This build-up of actin physically deforms the nucleus, and YAP (yes-associated protein), a gene regulator normally held in the cytoplasm, moves into the nucleus. Once inside, YAP switches on transcription, driving IL-2 expression and full T cell activation. The pathway depends on actin polymerisation rather than myosin contraction: blocking actin polymerisation with cytochalasin D broke the whole chain, while blocking myosin with blebbistatin made little difference. This sets T cells apart from most other cell types, which rely on myosin-driven contractile force instead. Integrins, rather than the T cell receptor itself, turned out to be the main sensor of ECM stiffness in this system^[6].

No study has directly tested this specific molecular pathway, integrin engagement driving actin polymerisation, nuclear deformation and YAP translocation, in $\gamma\delta$ T cells, although the functional consequences of matrix mechanics on $\gamma\delta$ T cell biology are starting to be documented. A recent preprint

from Obuseh and colleagues, using tunable collagen-based matrices of controlled viscoelasticity, found that matrix viscoelastic properties directly shape $\gamma\delta$ T cell migration, differentiation state and effector function, with accompanying proteomic evidence implicating actin remodelling and metabolic pathways^[7]. This is an important result and, at the time of writing, an unreviewed preprint, but it is also, on its own terms, functional rather than mechanistic: it establishes that $\gamma\delta$ T cells respond to matrix viscoelasticity without establishing whether that response runs through integrin engagement specifically, whether it involves the actin-nuclear deformation-YAP axis mapped in $\alpha\beta$ T cells, or whether different $\gamma\delta$ subsets rely on different mechanisms. The gap this review is describing is therefore better stated with that qualification built in: functional sensitivity to matrix mechanics is now documented in $\gamma\delta$ T cells^[7], but the molecular transduction pathway underlying it, and whether it is the same pathway already characterised in $\alpha\beta$ T cells^[6], remains untested. This is a striking gap given that $\gamma\delta$ T cells sit at unusually high density in ECM-rich barrier tissues^[4] and already express ECM-binding integrins, from CD103 and CD49a specifically^[5] to the broader repertoire described above^[3]. This matters practically as well as academically, because $\gamma\delta$ T cells are currently being developed as cancer immunotherapy agents. Knowing whether they respond to ECM stiffness the way $\alpha\beta$ T cells do, and through which molecular route, would directly inform how to engineer them to get into stiff tumour tissue, a point returned to later in this review.

It is also worth separating this ECM-mechanosensing question cleanly from a different and better-studied form of mechanosensing in T cells: TCR mechanosensing, in which the T cell receptor itself acts as a mechanosensor, with force applied through an engaged antigen contact altering TCR conformation and triggering signalling independently of any integrin or ECM contact. The pathway discussed throughout this review, integrin engagement with ECM components feeding through actin and the nucleus to YAP, is mechanistically distinct from TCR mechanosensing: it does not require antigen recognition, and in $\alpha\beta$ T cells Feng and colleagues showed it proceeds through integrins rather than the TCR^[6]. Because $\gamma\delta$ T cells are unusual in being able to recognise antigen independently of MHC restriction and, in some cases, through TCR-independent activation altogether, conflating ECM mechanosensing with TCR mechanosensing in this lineage would be a particularly easy mistake to make, and it is not always kept distinct in the existing literature. Future experimental work on $\gamma\delta$ T cell mechanobiology needs to isolate the ECM/integrin route from the TCR route explicitly, for example by comparing responses to ECM substrates of varying stiffness in the presence and absence of TCR

engagement, rather than treating any force-dependent $\gamma\delta$ T cell response as evidence for one pathway or the other by default.

The relationship between $\gamma\delta$ T cells and the ECM is also not only outside-in. Ruta and colleagues, studying the foreign body response to implanted biomaterials, showed that $\gamma\delta$ T cells actively shape the surrounding stroma, with their presence altering local matrix composition and vascularity, indicating that $\gamma\delta$ T cells are not just responders to a pre-existing matrix but active participants in building the one they subsequently occupy^[8]. That finding is one-directional, from $\gamma\delta$ T cell to stroma, and does not by itself demonstrate the reverse arm, ECM properties feeding back to change $\gamma\delta$ T cell state. Read alongside the outside-in evidence already discussed, integrin-dependent adhesion, viscoelasticity-dependent effector function, and the still-hypothetical mechanotransduction pathway, it raises the further possibility of a genuine bidirectional feedback loop, in which $\gamma\delta$ T cells remodel the matrix, the remodelled matrix in turn changes $\gamma\delta$ T cell state through the pathway this review is concerned with, and that altered state feeds back into further remodelling. That bidirectional loop is this review's own extension of the evidence, not an established finding: Ruta and colleagues demonstrated the $\gamma\delta$ -to-stroma direction only, and closing the loop experimentally would need the same integrin/YAP readouts proposed throughout this review, measured in a matrix that the $\gamma\delta$ T cells themselves have already begun to remodel.

$\gamma\delta$ T cells at barrier tissues: the gut

Intestinal intraepithelial lymphocytes (IELs) sit at the interface between the intestinal lumen, which is constantly exposed to food and microbes, and the rest of the body. Sullivan and colleagues showed that this position works in both directions: $\gamma\delta$ T cells regulate the epithelium's response to dietary nutrients by suppressing interleukin-22 (IL-22) production from type 3 innate lymphoid cells, while the transcriptome and tissue location of the $\gamma\delta$ T cells themselves change depending on what is being eaten^[9]. This shows that $\gamma\delta$ IELs pick up on environmental signals, including diet, and feed them into epithelial remodelling, and that they are clearly sensitive to changes in their surroundings. What it does not show is whether that sensitivity reaches down to the physical structure of the tissue itself, the basement membrane and collagen scaffold that the epithelium and its resident lymphocytes are sitting on.

How IELs respond to microbes in the gut lumen has been studied using high-resolution microscopy and genetic tools in unusual detail. Hoytema van Konijnenburg and colleagues found that TCR $\gamma\delta$ IELs move

and position themselves in the epithelium in a specific pattern, one that is shaped directly by the microbiota. Using intravital microscopy in TCR $\gamma\delta$ reporter mice, they showed that $\gamma\delta$ IELs travel almost entirely in the narrow space between the epithelial layer and the basement membrane, patrolling the villus rather than sitting still. Under normal conditions in naive mice, $\gamma\delta$ IELs kept moving continuously, each cell covering roughly 950 μm^2 of villus surface per hour at around 6 μm per minute, and this movement followed a set pattern rather than happening at random. In germ-free mice, that pattern broke down: coverage dropped, and the up-and-down movement between villus tip and crypt almost disappeared. Reintroducing commensal microbiota brought the patrolling back. This shows that the microbial environment is actively directing how $\gamma\delta$ T cells move, rather than that pattern being something built into the cell itself.

When mice were infected with *Salmonella* Typhimurium or *Toxoplasma gondii*, $\gamma\delta$ IEL behaviour changed sharply within two hours. The smooth patrolling gave way to quick, angled movements in and out between neighbouring epithelial cells, dipping down into the gap between two cells, coming back up, and moving across to the next gap, a motion the authors call flossing. Flossing clustered at hotspots near where the pathogen was present. Using mice with an inducible, epithelial-cell-specific knockout of Myd88, the authors showed that this response depended on the surrounding epithelial cells sensing the microbe, not on the $\gamma\delta$ T cells sensing it themselves. Blocking the $\gamma\delta$ TCR did not stop flossing, which confirms that epithelial cells detect the pathogen and signal outward to direct $\gamma\delta$ IEL behaviour, largely without needing the TCR at all^[10].

This work maps $\gamma\delta$ IEL behaviour and the epithelial signalling behind it in exceptional detail, but the mechanical properties of the basement membrane the cells are patrolling along are never examined. Gray and colleagues have already shown that gut-resident $\gamma\delta$ T cells express the ECM-binding integrins CD103 and CD49a, so the physical hardware for direct ECM engagement is there^[5]. Whether the mechanotransduction chain that Feng and colleagues mapped in $\alpha\beta$ T cells also operates here, and whether ECM stiffness or basement-membrane remodelling changes $\gamma\delta$ IEL motility, patrolling coverage, or the flossing response during infection, has not been tested. Since infection and inflammation are already known to remodel the intestinal basement membrane and change its stiffness, this is a gap that could actually be closed rather than a purely theoretical one: the same intravital imaging used to characterise flossing could be combined with genetic or pharmacological manipulation of basement-membrane stiffness to find out whether the mechanical route matters as much as the chemical one.

This gap has a direct clinical counterpart. Inflammatory bowel disease is defined partly by pathological remodelling of the same subepithelial basement membrane that gut $\gamma\delta$ IELs patrol, thickening and stiffening through excess collagen deposition and cross-linking during chronic inflammation. If CD103- and CD49a-mediated ECM engagement is what lets $\gamma\delta$ IELs maintain their patrolling coverage and infection-responsive flossing, as the hardware described above would predict, then a stiffened, fibrotic IBD basement membrane is a plausible, testable driver of impaired $\gamma\delta$ IEL surveillance, a mechanism distinct from the cytokine-driven barrier dysfunction that dominates current IBD models. This also identifies where current IBD immunotherapy sits relative to this pathway. Vedolizumab, the gut-selective biologic most widely used in IBD, works by blocking $\alpha 4\beta 7$ integrin, which governs how circulating lymphocytes enter gut tissue in the first place, not the CD103/CD49a-mediated retention and matrix engagement that operates once a $\gamma\delta$ IEL is already resident in the epithelium^[11]. A therapy targeting the latter pathway would be mechanistically distinct from, and potentially complementary to, existing gut-selective biologics, but nothing in the current literature establishes whether restoring or protecting $\gamma\delta$ IEL matrix engagement in a fibrotic gut would help or simply be irrelevant to disease control.

$\gamma\delta$ T cells at barrier tissues: the skin

The skin is an even clearer case of unexamined ECM engagement, because here the resident $\gamma\delta$ T cell population is not just present in the tissue but visibly shaped by it. In adult mice, $\gamma\delta$ T cells are split across tissues, with the large majority, around 95%, sitting in the epidermis. Almost all of these epidermal $\gamma\delta$ T cells belong to a single, invariant population called dendritic epidermal T cells (DETCs), named because, unlike the rounded lymphocytes found in blood or lymph node, they send out long dendritic processes between the surrounding keratinocytes^[12]. These dendrites are not a passive resting shape. They are actively held in place through continuous contact with the basal keratinocyte layer and its basement membrane, and DETCs use them to cover a much larger area of epithelium than their cell body alone would allow, pulling them back and reforming them when there is local tissue damage^[13].

This dendritic shape is itself indirect evidence that the ECM is instructing the cell's form, since the same basement membrane components, laminin and collagen among them, that Gray and colleagues showed are bound by CD49a on V δ 1 cells elsewhere in the body, are what DETC dendrites extend across and adhere to here^[5]. DETCs also depend on E-cadherin contacts with keratinocytes, which is a junctional form of adhesion rather than pure ECM contact, but still runs through much of the same cytoskeletal and integrin-linked machinery used for ECM engagement^[13]. After injury, DETCs are among the first cells to

detect the damage: they pull back their dendrites, round up, migrate to the wound edge, and secrete keratinocyte growth factors that help drive re-epithelialisation and wound closure^[12]. It's worth noting that DETCs as such are a mouse-specific system; human skin does not have an exact equivalent invariant population, and human cutaneous $\gamma\delta$ T cells are instead a more mixed group of subsets that still occupy the same epidermal and dermal ECM niches and are involved in comparable roles in skin immunity and disease^[14]. So the ECM-engagement questions raised here for DETCs apply, in a modified form, to the human cutaneous $\gamma\delta$ compartment too, even though the exact dendritic morphology described is specific to the mouse model. This wound-healing role is one of the best-established functions of any $\gamma\delta$ T cell subset, and it is fundamentally a response to a tissue in which both the ECM and the epithelium sitting on it have been physically torn. Yet the literature on it is written almost entirely in terms of soluble growth factors and cytokines, not in terms of how DETCs mechanically detect the loss of matrix integrity that precedes those signals.

No study has asked whether DETC dendrite retraction after injury is itself a mechanotransductive response, of the kind Feng and colleagues described for $\alpha\beta$ T cells, to a sudden loss of substrate stiffness or continuity, rather than only a chemical response to alarmins released by keratinocytes. Nor has any study asked whether the basal keratinocyte basement membrane, which stiffens with age and in chronic inflammatory skin disease in a way that broadly parallels the age-related rise in CD103 and CD49a that Gray and colleagues saw in gut V δ 1 cells, drives similar changes in DETC integrin expression or function over a lifetime^[5]. The skin may be one of the easiest systems in which to close the gap this review is describing, because DETC morphology already gives a visible, measurable readout of matrix engagement, one that has simply never been connected to the molecular mechanotransduction pathway now established in conventional T cells.

This mechanotransductive framing also gives a testable explanation for a treatment already in routine clinical use. Negative pressure wound therapy accelerates healing in many chronic wounds, and while its established mechanisms are mechanical fluid clearance and enhanced angiogenesis, a recent mechanobiological re-analysis argues that the applied strain field itself is a direct signal to the cells in the wound bed, not merely a side effect of suction^[15]. If DETC dendrite retraction and re-extension is mechanotransductive in the way proposed above, negative pressure wound therapy would be expected to alter resident $\gamma\delta$ T cell integrin engagement and, if the Feng and colleagues pathway is conserved, nuclear YAP localisation, at the wound edge, which would make part of its clinical benefit an unrecognised effect on local $\gamma\delta$ T cell activation rather than only on fibroblasts, endothelium and fluid dynamics. This is

directly testable: comparing DETC or human cutaneous $\gamma\delta$ T cell integrin engagement and YAP localisation at the margin of negative-pressure-treated wounds against standard-dressing controls would show whether this mechanism contributes, and could help explain why negative pressure wound therapy benefits some chronic wounds, such as diabetic foot ulcers, more reliably than others.

$\gamma\delta$ T cells in neuroinflammatory disease

The role of $\gamma\delta$ T cells in neuroinflammatory disease is where the lack of a defined ECM-sensing mechanism stops being just a conceptual gap and becomes clinically relevant. In traumatic brain injury (TBI), $\gamma\delta$ T cells show opposing functions depending on subset. Abou-El-Hassan and colleagues showed that V γ 4 $\gamma\delta$ T cells infiltrate the brain and secrete interferon- γ (IFN- γ) and interleukin-17 (IL-17), activating microglia and driving neuroinflammation, while V γ 1 $\gamma\delta$ T cells secrete transforming growth factor- β (TGF- β), which maintains microglial homeostasis and reduces TBI pathology instead^[16]. Two $\gamma\delta$ subsets with the same basic receptor structure producing opposite outcomes in the same injured tissue suggests that separate molecular programmes are driving their activation and differentiation, and it raises a question nobody has tested: whether differential ECM engagement is part of what separates them. TBI is, at the tissue level, an injury defined by damage to the brain's specialised perivascular and basement-membrane ECM, so it would be somewhat surprising if the two subsets encountered that damaged matrix in exactly the same way.

In experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis, $\gamma\delta$ T cells show disease-related changes: their numbers in the central nervous system (CNS) rise during the acute phase, and depleting them significantly reduces clinical severity, inflammation and demyelination at that stage, with weaker effects later in the chronic phase^[17]. What controls $\gamma\delta$ T cell recruitment and retention in the CNS during neuroinflammatory disease, including any role for ECM-dependent adhesion, is still not well defined by this or later work. The blood-brain barrier (BBB) is one of the most specialised ECM-rich structures in the body, built from tightly regulated basement membranes and tight-junction complexes maintained jointly by endothelial cells, pericytes and astrocytic end-feet. How $\gamma\delta$ T cells cross this barrier compared with $\alpha\beta$ T cells, and whether they use different adhesion or mechanosensing mechanisms to do it, has barely been looked at directly. Immune cells entering the CNS both respond to the local ECM and remodel it through matrix metalloproteinase (MMP) expression, so this is not a side issue in CNS immunology, it sits close to the centre of it: the same basement membrane whose stiffness and composition are known to gate leukocyte entry generally has never been checked specifically for its

effect on V γ 4 versus V γ 1 trafficking, despite how differently these two subsets behave once they are inside the tissue.

Both of these findings sit next to an existing, approved precedent for adhesion-blockade therapy in CNS disease. Natalizumab, which blocks the α 4 integrin subunit shared by VLA-4 and α 4 β 7, prevents lymphocyte entry across the blood-brain barrier and is an effective treatment for relapsing multiple sclerosis, but it does so indiscriminately, blocking every α 4-integrin-dependent lymphocyte regardless of whether that cell would have been pathogenic or protective once inside the tissue^[18]. That blunt precedent throws the V γ 4/V γ 1 finding into sharper relief. If pathogenic V γ 4 and protective V γ 1 $\gamma\delta$ T cells rely on different integrins, or engage a differently stiffened or differently composed perivascular basement membrane during TBI, as the tissue-level damage to that ECM would make plausible, a subset-selective adhesion-blocking strategy becomes conceivable in a way that pan- α 4 blockade cannot achieve, since natalizumab-type therapy cannot distinguish a harmful infiltrating subset from a beneficial one. This is a concrete, testable extension of the existing finding: characterising the integrin repertoire and ECM-engagement behaviour of V γ 4 versus V γ 1 cells specifically, rather than treating $\gamma\delta$ T cells as a single population, would establish whether selective rather than blanket adhesion blockade is a realistic route to separating the harmful and protective arms of the $\gamma\delta$ response in TBI and, potentially, in the EAE/MS setting where a similar CNS-entry step is already a validated drug target.

$\gamma\delta$ T cells in the tumour microenvironment

In cancer, an incomplete understanding of $\gamma\delta$ T cell ECM sensing matters even more directly, because it bears on a therapy that is already being tested in patients. $\gamma\delta$ T cells are strongly cytotoxic against many different cancer cell types in an MHC-independent way, which has made them attractive for adoptive cell therapy and other forms of cancer immunotherapy. But their effectiveness against solid tumours has been inconsistent, largely because of the immunosuppressive tumour microenvironment (TME) that surrounds most solid cancers^[4]. Much of that immunosuppression is mechanical and structural rather than purely chemical. Solid tumours typically build a dense, cross-linked collagen network, stiffened by the same LOX-family enzymes discussed earlier in the context of inflamed skin, and this network physically blocks immune cell infiltration and helps the tumour evade the immune system^[2].

The tumour ECM is not just denser, it is also chemically altered in ways that reprogramme the immune cells around it. Tarantola and colleagues showed that glycan modifications to the ECM in triple-negative breast cancer shape the innate and adaptive immune microenvironment, and that enzymatically editing

these tumour ECM glycans reprogrammes tumour-associated myeloid cells and improves conventional T cell infiltration and function^[19]. Whether $\gamma\delta$ T cells respond the same way to this kind of ECM change, whether they are equally blocked by dense collagen and equally helped by glycan-editing, or whether their different integrin set and possibly different mechanotransduction machinery give them an advantage or disadvantage getting through such a matrix, is not addressed anywhere in the literature. $\gamma\delta$ T cells are increasingly being tested as cellular immunotherapy products, including in early-phase clinical trials of adoptively transferred and engineered $\gamma\delta$ T cells, but designing them to get into stiff, glycan-altered tumour matrices is currently limited by one basic fact: nobody has established whether $\gamma\delta$ T cells even have the integrin-actin-YAP mechanotransduction axis that Feng and colleagues mapped in $\alpha\beta$ T cells, let alone whether it could be tuned^{[6][4]}. Closing this gap would complete the basic biology and also give a concrete engineering target, similar to choosing a co-stimulatory domain in CAR T cell design, for improving how well $\gamma\delta$ T cells persist and function inside mechanically hostile tumours. This matters particularly because most current $\gamma\delta$ T cell immunotherapy platforms expand and infuse the circulating V γ 9V δ 2 subset^[4], which, based on the tissue-residency reasoning set out earlier, is the subset least likely to have evolved a dedicated ECM mechanosensing programme in the first place. If tissue-resident V δ 1 cells turn out to have a stronger integrin-actin-YAP axis than V γ 9V δ 2 cells, that would argue for changing which cell product is used, not only how the matrix is engineered, for solid-tumour treatment.

The assumption that simply softening the tumour matrix will let more immune cells in also needs to be treated carefully rather than as a self-evidently good therapeutic strategy. Simtuzumab, an antibody against the LOX-family enzyme LOXL2 that was specifically designed to reduce pathological collagen cross-linking, failed to improve outcomes when added to gemcitabine in a randomised phase II trial in metastatic pancreatic cancer, despite strong preclinical rationale^[20]. That failure is a caution against assuming that de-stiffening a tumour's ECM will automatically translate into better immune control: it matters just as much what the immune cells that reach a softened matrix are then able to do once they get there. This is exactly where a defined $\gamma\delta$ T cell mechanotransduction pathway would earn its keep as a companion biomarker for LOX-directed therapy, rather than as an argument for LOX inhibition on its own: if $\gamma\delta$ T cells specifically require a stiffness-dependent integrin-actin-YAP signal to become and stay activated, then softening the matrix without also supplying that mechanical activation cue could leave infiltrating $\gamma\delta$ T cells present but functionally quiescent, which would be consistent with simtuzumab's clinical failure without requiring any change to the drug's stated mechanism.

A newer and more direct link is now available too. VT3989, an oral inhibitor of TEAD palmitoylation that blocks YAP-dependent transcription, has produced genuine clinical responses in a phase 1/2 trial in mesothelioma and other solid tumours, working by shutting down the same YAP-dependent transcriptional programme that these tumours depend on for growth^[21]. If $\gamma\delta$ T cells activate through integrin-actin-YAP signalling in the same way Feng and colleagues showed for $\alpha\beta$ T cells, then a drug designed to block tumour-intrinsic YAP could simultaneously blunt the mechanotransductive activation of any $\gamma\delta$ T cell, endogenous or adoptively transferred, trying to respond to that same tumour, an on-target interaction between a promising oncology drug and T cell mechanobiology that has not been examined because the T cell side of the pathway has never been established in this lineage. Testing $\gamma\delta$ T cell YAP activation status directly in biopsies from patients on YAP/TEAD-inhibitor trials would establish whether this is a real concern, and if it is, would argue for scheduling or dosing strategies that separate tumour-cell YAP blockade from periods of active $\gamma\delta$ T cell engagement, rather than assuming the two can simply be combined.

The central gap

Putting the sections above together, a consistent pattern shows up. $\gamma\delta$ T cells are known, in exact molecular detail in some cases, to physically contact the ECM: they express a broad integrin repertoire, from the $\beta 1$, $\beta 2$ and $\beta 7$ families generally^[3] to CD103 and CD49a specifically, which bind E-cadherin and collagen respectively, with expression that rises with age and follows tissue-specific patterns matching where different $\gamma\delta$ subsets live^[5]. They are also known, in considerable behavioural detail, to change their movement, shape and function in response to their surroundings, whether that is diet and epithelial IL-22 signalling in the gut^[9], microbiota-dependent patrolling and infection-triggered flossing in the intestinal epithelium^[10], dendrite retraction and re-epithelialisation after skin injury^[12], opposing inflammatory programmes in the injured brain^[16], infiltration and demyelination in the inflamed spinal cord^[17], or, most recently, altered migration, differentiation and effector function on viscoelastically tuned matrices in vitro^[7]. And separately, entirely outside the $\gamma\delta$ field, it is known that $\alpha\beta$ T cells turn physical contact with a stiff ECM into a defined internal signal: integrin engagement drives actin polymerisation, nuclear deformation, YAP translocation and IL-2-dependent activation, through a pathway that does not need the T cell receptor at all^[6].

What has never been put together is the middle piece connecting these three areas: a demonstration that $\gamma\delta$ T cell integrin engagement with the ECM feeds into the same defined intracellular signal that shapes T cell behaviour in the $\alpha\beta$ lineage, or indeed into any equivalently defined mechanical signal. Every one of the $\gamma\delta$ behaviours listed above, patrolling speed, flossing, dendrite shape, cytokine balance, tumour infiltration, has been explained either by soluble signals (cytokines, growth factors, alarmins) or by TCR-dependent antigen recognition; even the new viscoelasticity data, encouraging as it is, documents a functional response without yet identifying its molecular route^[7]. In every case, the possibility that direct, TCR-independent mechanical sensing of the ECM runs through the specific integrin-actin-YAP route mapped in $\alpha\beta$ T cells has simply not been tested. This is not a small gap in an otherwise complete picture. Because $\gamma\delta$ T cells sit disproportionately at exactly the barrier and injury sites where ECM mechanics change the fastest and the most, over hours during infection, over years with ageing, over the course of tumour growth, a mechanosensing pathway like the one mapped in $\alpha\beta$ T cells would be expected to matter at least as much here, probably more.

The gap is also uneven in a useful way. On one side is a mature, mechanistic literature, built almost entirely in $\alpha\beta$ T cells and non-immune cells, where the molecular players (integrins, F-actin, the nuclear envelope, YAP) are named and their order of events established through direct pharmacological testing^[6]^[1]. On the other side is an equally mature but purely descriptive literature on $\gamma\delta$ T cell behaviour at barrier tissues, full of carefully measured phenotypes, patrol speed, coverage area, dendrite number, cytokine ratio, but silent on mechanism in places where the mechanism could plausibly be mechanical rather than only chemical^{[10][12][16]}. These two literatures have simply never met. Not because anyone tested the connection and ruled it out, but because mechanobiology and $\gamma\delta$ T cell immunology have grown up as separate fields, using different model systems and different traditions. Seeing this as a gap caused by fields not talking to each other, as much as a gap in data, is useful in itself, because it suggests that closing it might only need fairly modest new experiments, applying tools that already exist in mechanobiology to $\gamma\delta$ T cell model systems that already exist, rather than inventing anything new.

Framed this way, the gap is not only a missing piece of basic biology, it is what stands between several already-identifiable clinical hypotheses and the experiments that could test them: whether basement-membrane fibrosis in inflammatory bowel disease degrades $\gamma\delta$ IEL surveillance in a way current gut-selective biologics do not address; whether negative pressure wound therapy's clinical benefit is partly mediated through $\gamma\delta$ T cell mechanotransduction at the wound edge; whether V γ 4 and V γ 1 cells in traumatic brain injury could be separated by a subset-selective adhesion-blocking strategy in a way pan-

integrin drugs such as natalizumab cannot achieve; and whether YAP/TEAD-inhibitor cancer therapies carry an unrecognised, on-target risk to $\gamma\delta$ T cell activation in the tumours they are meant to help treat. None of these hypotheses can be tested without first establishing whether the basic mechanotransduction pathway exists in $\gamma\delta$ T cells at all, which is why that remains the single experiment this review keeps returning to.

Future directions

A few concrete experiments follow directly from the gap described above. The most obvious is to test whether the integrin-actin-YAP-IL-2 axis that Feng and colleagues described in $\alpha\beta$ T cells is present, absent, or different in $\gamma\delta$ T cell subsets, using the same substrates of controlled stiffness, the same drugs (cytochalasin D and blebbistatin), and the same YAP-translocation readouts, but applied to sorted V δ 1, V δ 2 and DETC populations rather than to bulk T cells. Since V δ 1 cells already express CD49a and CD103 at levels that vary by tissue and age^[5], this same comparison could also ask whether the amount of integrin expressed predicts how strong the mechanotransductive response is, which would give a testable, quantitative link between the adhesion pattern that is already well described and the signalling that is not.

A second direction would take the intravital imaging methods already used to study gut $\gamma\delta$ IEL patrolling and flossing^[10] and pair them with pharmacological or genetic manipulation of basement-membrane stiffness or cross-linking, for example through LOX inhibition, to see whether patrolling coverage, patrol speed, or the flossing response to infection are gated mechanically as well as chemically. The same idea applies especially well to the skin, where DETC dendrite shape already gives a visible, measurable proxy for matrix engagement^[13]. Live imaging of dendrite behaviour on substrates of controlled stiffness, before and after a simulated injury, would directly test whether dendrite retraction is a mechanotransductive event rather than something driven purely by cytokines.

Third, single-cell and spatial transcriptomic approaches, of the kind Gray and colleagues have already started applying to human $\gamma\delta$ T cells^[5], could be searched specifically for mechanosensor and mechanotransduction-pathway genes, including Piezo1 and downstream YAP targets, to work out which $\gamma\delta$ subsets are most likely to have a working mechanosensing pathway before committing to slower functional experiments. Finally, in cancer immunotherapy, engineered $\gamma\delta$ T cell products could be tested directly for how well they get into collagen-dense tumour matrices of varying stiffness and glycan

composition in vitro, of the kind Tarantola and colleagues described^[19], both to see how they behave now and to check whether engineering strategies that tune the integrin-actin-YAP axis, assuming it exists in $\gamma\delta$ T cells, improve infiltration and persistence. Together, these experiments would turn the gap described in this review into a concrete, testable research programme.

Two design features deserve to be built into that programme from the start rather than added afterwards. First, any of the stiffness- or viscoelasticity-manipulation experiments above should be run in parallel with a TCR-blocked or antigen-free condition, so that a force-dependent $\gamma\delta$ T cell response can be attributed specifically to the ECM/integrin route rather than left ambiguous with TCR mechanosensing, extending the viscoelasticity work of Obuseh and colleagues by adding the integrin- and TCR-isolating controls it does not yet include^[7]. Second, testing the bidirectional feedback loop this review has proposed, in which $\gamma\delta$ T cells remodel the matrix and the remodelled matrix then acts back on $\gamma\delta$ T cell state, would mean combining the stromal-remodelling readouts Ruta and colleagues used in the foreign body response with the integrin/YAP readouts proposed above in the same longitudinal system, rather than treating $\gamma\delta$ -to-stroma and stroma-to- $\gamma\delta$ effects as two separate experiments^[8].

Beyond establishing the basic pathway, each of the disease-specific hypotheses raised above suggests its own direct experiment. In an IBD setting, comparing $\gamma\delta$ IEL patrolling coverage, flossing behaviour and CD103/CD49a engagement between healthy and fibrotic, basement-membrane-thickened intestinal tissue, using the same intravital and single-cell tools already applied to infection, would test whether matrix stiffening degrades IEL surveillance independently of cytokine-driven barrier dysfunction. In chronic wounds, comparing $\gamma\delta$ T cell integrin engagement and YAP localisation at the margins of negative-pressure-treated and conventionally dressed wounds would test whether part of negative pressure wound therapy's benefit runs through this pathway^[15]. In TBI, profiling the integrin repertoire of V γ 4 versus V γ 1 cells and the local perivascular ECM they each engage would establish whether a subset-selective adhesion-blocking strategy, distinct from pan- α 4 approaches such as natalizumab, is a realistic therapeutic route^[18]. And in the growing YAP/TEAD-inhibitor oncology pipeline, directly measuring $\gamma\delta$ T cell YAP activation status in tumour biopsies from patients on trials of drugs such as VT3989 would establish whether these agents carry an on-target cost to anti-tumour $\gamma\delta$ T cell function that current trial designs are not set up to detect^[21].

Conclusion

$\gamma\delta$ T cells sit directly on the extracellular matrix at almost every site where they are found in the body, through an integrin repertoire that is already reasonably well catalogued^[3]: gripping collagen and E-cadherin through CD49a and CD103 in the gut, sending dendrites across the keratinocyte basement membrane in the skin, crossing a basement-membrane-rich blood-brain barrier in neuroinflammatory disease, and meeting a stiffened, glycan-altered collagen network in solid tumours. Recent evidence also shows that $\gamma\delta$ T cells respond functionally to matrix viscoelasticity^[7] and actively remodel the stroma around them, raising the possibility of a bidirectional feedback loop with the matrix rather than a purely one-way relationship^[8]. What has not been established in any of these settings, and what this review has argued is a distinct and narrower question from either the adhesion literature or the functional viscoelasticity data, is whether that physical contact is read out through a dedicated mechanotransduction pathway of the kind now defined in conventional $\alpha\beta$ T cells, where integrin engagement drives actin polymerisation, nuclear deformation, YAP translocation and IL-2-dependent activation independently of both the T cell receptor and TCR-mediated mechanosensing. Closing this gap would fill in a basic and overdue part of $\gamma\delta$ T cell biology, and it would also resolve a set of concrete clinical questions that already have plausible answers waiting to be tested: whether IBD-associated basement-membrane fibrosis degrades protective $\gamma\delta$ IEL surveillance, whether negative pressure wound therapy works partly by mechanically activating resident $\gamma\delta$ T cells, whether a subset-selective adhesion-blocking strategy could separate the harmful and protective arms of the $\gamma\delta$ response in traumatic brain injury where pan-integrin drugs such as natalizumab cannot, and whether the YAP/TEAD-inhibitor drugs now entering oncology practice carry an unrecognised cost to the very $\gamma\delta$ T cells being recruited or engineered to fight the tumours they target. Each of these questions follows directly from establishing the basic mechanotransduction pathway this review argues has been overlooked, which is what makes that first experiment worth doing.

References

1. ^a ^bMiller AE, Hu P, Barker TH (2020). "Feeling Things Out: Bidirectional Signaling of the Cell-ECM Interface, Implications in the Mechanobiology of Cell Spreading, Migration, Proliferation, and Differentiation." *Adv Health Mater.* 9(8):1901445.

2. ^a ^b ^c Sutherland TE, Dyer DP, Allen JE (2023). "The Extracellular Matrix and the Immune System: A Mutually Dependent Relationship." *Science*. **379**(6633):eabp8964.
3. ^a ^b ^c ^d ^e Siegers GM (2018). "Integral Roles for Integrins in $\gamma\delta$ T Cell Function." *Front Immunol*. **9**:521.
4. ^a ^b ^c ^d ^e ^f ^g Hu Y, Hu Q, Li Y, Lu L, Xiang Z, Yin Z, Kabelitz D, Wu Y (2023). " $\gamma\delta$ T Cells: Origin and Fate, Subsets, Diseases and Immunotherapy." *Signal Transduct Target Ther*. **8**(1):434.
5. ^a ^b ^c ^d ^e ^f ^g ^h Gray JJ, Caron DP, Wells SB, Guyer R, Szabo P, Rainbow D, Ergen C, Rybkina K, Bradley MC, Matsumoto R, Pethe K (2024). "Human $\gamma\delta$ T Cells in Diverse Tissues Exhibit Site-Specific Maturation Dynamics Across the Life Span." *Sci Immunol*. **9**(96):eadn3954.
6. ^a ^b ^c ^d ^e ^f Feng J, Zhao G, Zhao L, Geng L, Zhang S, Xu L, Liu M, Zhang G, Xu F, Lin M, Guo H (2026). "Integrin-Mediated Mechanosensing of Modeled Lymph Node Microenvironment Promotes T Cell Activation via Nuclear Deformation." *Research*. **9**:1121.
7. ^a ^b ^c ^d ^e ^f Obuseh FO, Chang M, Price J, Ruark K, To T, Lourenco L, Budnik B, Mooney D (2026). "Viscoelastic Niches Shape $\gamma\delta$ T-Cell Phenotype and Effector Function." *bioRxiv*. doi:10.64898/2026.07.23.740350.
8. ^a ^b ^c Ruta A, Krishnan K, Woo J, Mejías JC, Gray-Gaillard EF, Maestas DR Jr, Nguyen HH, Rindone AN, Cherry C, Patatanian M, Yu FH, Yang B, Amelung C, King CD, Schilling B, Gerecht S, Fertig EJ, Huyer LD, Pardoll DM, Elisseeff JH (2026). " $\gamma\delta$ T Cell-Stromal Networks Modulate Matrix Composition and Vascularity in Foreign Body Response." *Nat Commun*. **17**:5334.
9. ^a ^b Sullivan ZA, Khoury-Hanold W, Lim J, Smillie C, Biton M, Reis B, Zwick RK, Pope SD, Israni-Winger K, Parasa R, Philip N, Rashed S, Palm N, Wang A, Mucida D, Regev A, Medzhitov R (2021). " $\gamma\delta$ T Cells Regulate the Intestinal Response to Nutrient Sensing." *Science*. **371**(6535):eaba8310.
10. ^a ^b ^c ^d Hoytema van Konijnenburg DPH, Reis BS, Pedicord VA, Farache J, Victora GD, Mucida D (2017). "Intestinal Epithelial and Intraepithelial T Cell Crosstalk Mediates a Dynamic Response to Infection." *Cell*. **171**(4):783–794.
11. ^a ^b Cherry LN, Yunker NS, Lambert ER, Vaughan D, Lowe DK (2015). "Vedolizumab: An $\alpha 4\beta 7$ Integrin Antagonist for Ulcerative Colitis and Crohn's Disease." *Therap Adv Chronic Dis*. **6**(5):224–233.
12. ^a ^b ^c ^d Hu W, Shang R, Yang J, Chen C, Liu Z, Liang G, He W, Luo G (2022). "Skin $\gamma\delta$ T Cells and Their Function in Wound Healing." *Front Immunol*. **13**:875076.
13. ^a ^b ^c Nielsen MM, Witherden DA, Havran WL (2017). " $\gamma\delta$ T Cells in Homeostasis and Host Defence of Epithelial Barrier Tissues." *Nat Rev Immunol*. **17**(12):733–745.
14. ^a ^b Cruz MS, Diamond A, Russell A, Jameson JM (2018). "Human $\alpha\beta$ and $\gamma\delta$ T Cells in Skin Immunity and Disease." *Front Immunol*. **9**:1304.

15. ^a ^bGefen A, Russo S, Ciliberti M (2024). "Revisiting Negative Pressure Wound Therapy from a Mechanobiological Perspective Supported by Clinical and Pathological Data." *Int Wound J.* **21**(12):e70098.
16. ^a ^b ^cAbou-El-Hassan H, Rezende RM, Izzy S, Gabriely G, Yahya T, Tatematsu BK, Habashy KJ, Lopes JR, de Oliveira GLV, Maghzi AH, Yin Z, Cox LM, Krishnan R, Butovsky O, Weiner HL (2023). "V γ 1 and V γ 4 Gamma-Delta T Cells Play Opposing Roles in the Immunopathology of Traumatic Brain Injury in Males." *Nat Commun.* **14**(1):4286.
17. ^a ^bRajan AJ, Gao YL, Raine CS, Brosnan CF (1996). "A Pathogenic Role for $\gamma\delta$ T Cells in Relapsing-Remitting Experimental Allergic Encephalomyelitis in the SJL Mouse." *J Immunol.* **157**(2):941–949.
18. ^a ^bRice GPA, Hartung H-P, Calabresi PA (2005). "Anti-Alpha4 Integrin Therapy for Multiple Sclerosis: Mechanisms and Rationale." *Neurology.* **64**(8):1336–1342.
19. ^a ^bTarantola L, Tyler EJ, Liu Y, Maniati E, Thornton KA, Martín-Otal C, Hanna D, Kumar R, Gauthier V, Hirani P, Ramos MB, Roth NJ, Bragg J, Puttock EH, McDermott J, Rajeeve V, Cutillas P, Maiques O, Soulier A, Correia de Sampaio P, Jones LJ, Davies DM, Maher J, Haslam SM, Läubli H, Pearce OMT (2026). "Glycosylated Extracellular Matrix Drives Immune Suppression by Modulating Macrophage-T Cell Crosstalk in Triple-Negative Breast Cancer." *Nat Commun.* **17**:5008.
20. ^aBenson AB, Wainberg ZA, Hecht JR, Vyushkov D, Dong H, Bendell J, Kudrik F (2017). "A Phase II Randomized, Double-Blind, Placebo-Controlled Study of Simtuzumab or Placebo in Combination with Gemcitabine for the First-Line Treatment of Pancreatic Adenocarcinoma." *Oncologist.* **22**(3):241–e15.
21. ^a ^bYap TA, Kwiatkowski DJ, Dagogo-Jack I, Offin M, Zauderer MG, Kratzke R, Desai J, Body A, Millward M, Tolcher AW, Raghav KPS, Thurston A, Post L, Dorr FA, Tang TT, Li Y, Sharma N, Kindler HL (2025). "YAP/TEAD Inhibitor VT3989 in Solid Tumors: A Phase 1/2 Trial." *Nat Med.* **31**(12):4281–4290.

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.