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Review

Integrins as Drug Targets in Vascular and Related Diseases

Emily Meredith [1,*], and Martin A. Schwartz [1,2,3]

[1] Yale Cardiovascular Research Center, Department of Internal Medicine (Cardiology), Yale University School of Medicine, New Haven, CT 06511, USA, martin.schwartz@yale.edu
[2] Department of Cell Biology, Yale School of Medicine, New Haven, CT 06520, USA.
[3] Department of Biomedical Engineering, Yale University, New Haven, CT 06511, USA.
* Correspondence: Emily.meredith@yale.edu

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Abstract: Integrins are transmembrane receptors that, as critical participants in a vast range of pathological processes, are potential therapeutic targets. However, in only a few cases has the promise been realized by drug approval. In this review, we briefly review basic integrin biology and participation in disease, challenges in the development of safe, effective integrin-targeted therapies, and recent advances that may lead to progress.

Keywords: Integrins; cardiovascular disease; integrin therapeutics

1. Introduction

Integrins are heterodimeric transmembrane receptors that bind extracellular matrix (ECM) proteins and counter receptors on other cells, thereby mediating cell migration, angiogenesis, inflammatory signaling and immune cell invasion [1]. There are 24 unique integrin dimers, each formed by pairing one of the 18 alpha (α) subunits with one of the 8 beta (β) subunits, generating receptors with distinct ligand-binding and signaling functions. Integrins connect to the actin cytoskeleton inside the cell through a network of linker proteins, among which talin is the most crucial. This linkage transmits force between the ECM and the cytoskeleton, conferring mechanical stability to cells and tissues.

In addition to binding ECM components such as fibronectin, vitronectin, collagen and laminin, integrins transmit signals to the cytoplasm through multiple adapters and signaling proteins, so-called outside-in signaling [2]. Conversely, binding of cytoplasmic proteins to integrin cytoplasmic tails can trigger a change in integrin conformation leading to increased affinity for extracellular ligands, termed inside-out signaling or activation. Integrin bidirectional signaling is highly dependent on complex conformational transitions that have been refined over 20 years of structural studies. In brief, bent, low-affinity integrins move through a series of steps to open, extended high affinity conformations; these conformational transitions are also dependent on mechanical loads such that tension promotes or stabilizes the extended, high affinity states [3]. In this way, integrins enable cells to both exert and sense ECM mechanical properties such as stiffness, loading and topography. Integrins transduce structural and mechanical variables into biochemical signals that guide a vast range of biological processes.

Reagents targeting GPCRs make up a staggering 40% of marketed drugs as of 2022 [4]. Here, specificity is enabled by the 850 GPCRs in the human genome and the extensive structural biology studies that have led to development of high affinity antagonists and agonists. New tools such as AlphaFold2, are further accelerating progress [5]. With only 24 integrins that often share subunits, development of successful integrin-targeting drugs is more challenging. Progress thus requires deeper understanding of both integrin

structural biology and functional biology in physiological and pathological processes.

While this review focuses on vascular and related diseases, we define these terms broadly, in keeping with the centrality of the vasculature to the physiology and pathology of nearly every other organ and system. Blood vessels control the growth and spread of cancers, the trafficking of leukocytes in inflammatory diseases, and health of many organs apart from basic functions of blood transport, hemostasis and repair. Thus, we will briefly review basic integrin expression, function and structural biology before covering contrasting successful and unsuccessful integrin therapies, where unsuccessful therapies fell short, and how we can move toward developing safe and effective integrin-targeted therapies.

2. Integrins in Disease

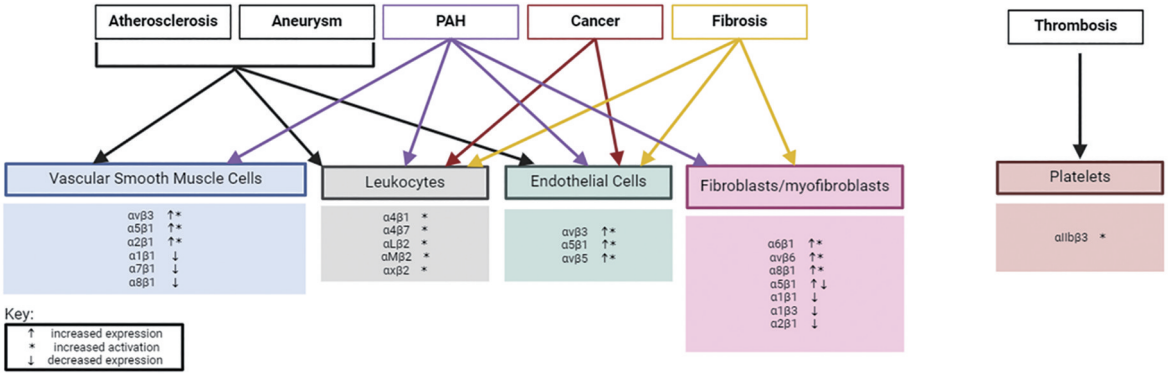

Figure 1. Regulation of integrins in vascular and related diseases. Atherosclerosis, aneurysms, pulmonary arterial hypertension (PAH), fibrosis, thrombosis and cancer involve multiple cell types in which altered integrin expression and/or function contribute to pathology. Endothelial cells (ECs), vascular smooth muscle cells (VSMCs), leukocytes, fibroblasts and platelets all change their integrin expression and activation profile in these disease states, α5β1 and αv integrins are upregulated and or activated in many of these settings, in keeping with their general roles in cell growth and migration during dynamic processes. The leukocyte integrins (β2 and α4 families) also contribute to inflammatory diseases via effects on leukocyte migration, activation and effector function. These integrins have this been the main targets for translational and clinical studies.

Vascular diseases in which integrins are central include atherosclerosis, thrombosis, pulmonary arterial hypertension (PAH) and thoracic and abdominal aortic aneurysms (TAA, AAA, respectively). The vasculature and integrins expressed therein also play supporting but important roles in other conditions, such as cancer, autoimmune disorders and fibrosis.

The endothelial cells that line the blood vessels control permeability and movement of leukocytes, mediate angiogenesis, control vascular tone and generally orchestrate blood vessel growth and function [6]. Fluid shear stress from blood flow exerts a major regulatory influence on endothelial phenotype, a process to which integrins substantially contribute [7]. Atherosclerosis arises selectively in regions of arteries under disturbed flow patterns (DSS). These regions are found at branch points and sites of high curvature, where changes in endothelial phenotype are associated with changes in integrin expression and ECM remodeling [8,9]. Both endothelial and smooth muscle compartments show increased expression and assembly of a fibronectin matrix in atherosclerosis, increased expression of fibronectin-binding integrins αvβ3 and α5β1, together with integrin activation, which together enhance inflammatory activation and plaque progression [10]. Importantly, inflamed endothelial cells express and activate Transforming Growth Factor-beta (TGFβ) signaling and undergo endothelial-mesenchymal transition (EndMT) under these conditions. Fibronectin and integrin α5 are both Smad2/3 target genes that are upregulated during EndMT [11] and blocking fibronectin-integrin signaling potently reduced atherosclerosis in mice [12,13]. The FN-integrin interaction and downstream signaling thus appears to be an important circuit within the TGFβ/EndMT/inflammatory cascade. Vascular smooth muscle cells (VSMCs) in the plaque also increase their expression of αvβ3 and α5β1 integrins, and decrease integrins associated with the contractile state, promoting phenotypic switching, migration into and proliferation in the plaque and TGFβ activation [14], creating an additional feed

forward mechanism that amplifies disease [15,16].

Infiltrating immune cells are equally important to the above diseases. T cells, macrophages and neutrophils are vital in tissue surveillance to detect damage and infection. This process requires their exit from the blood stream and subsequent migration through the tissue via integrins such as LFA-1 (αLβ2), Mac-1 (αMβ2), αxβ2, and α4β1 [17]. The migratory processes require integrins that bind their ligands with high affinity, thus, integrin activation is also critical for tissue inflammation, as well as other aspects of immunity. Inflammatory mediators trigger conversion of these integrins to the high affinity state to enable immune cell function [17]. In atherosclerosis, infiltrating monocytes are central to vessel inflammatory signaling. Blocking these processes is a viable approach for combatting pathological inflammation in, for example, autoimmune disease but the dangers of suppressing host pathogen defense must also be considered.

Major risk factors that can lead to the development of atherosclerosis include high blood pressure, elevated circulating cholesterol levels, and obesity. Other arterial diseases, including pulmonary arterial hypertension (PAH) and aneurysms, share both risk factors and pathological processes, and are often diagnosed concurrently or as co-morbidities [18–21]. In PAH, lung endothelial cells increase their integrin expression during artery narrowing associated with elevated blood pressure [22]. Endothelial cells upregulate integrin β5, while VSMCs upregulate αvβ3 [22,23]. Leukocytes, mainly activated macrophages and T cells, also infiltrate into remodeled pulmonary arteries of PAH patients associated with integrin activation [24].

A major component in atherosclerosis, hypertensive artery remodeling and cancer is fibrosis, mediated mainly by myofibroblasts. These cells derive from fibroblasts, which involves upregulation of integrin α5β1 as well as α6β1, αvβ6 and α8β1 and downregulating integrins associated with inactive fibroblasts [25,26] Myofibroblasts are the highly contractile and secretory cells that make the dense collagen matrix associated with fibrosis. Fibrosis is of course associated with disease states in many other organs, which involves similar transitions in integrin expression and function [27].

Aneurysms represent a form of pathological remodeling due to some combination of high blood pressure, mutations in ECM, contractile proteins and their regulators, and inflammation [28]. Integrin α5β1 on SMCs was found to be critical to the progression and rupture of aneurysms through the fibronectin-mediated inflammatory signaling cascade [29]. Integrin αvβ3 also makes an important contribution, involving both altered expression [30] and changes in its ability to bind ECM ligands due to induction of legumain in macrophages [31]. Finally, integrin-mediated infiltration of leukocytes, contributes to aneurysm instability and perpetuates the inflammatory environment [28].

In cancer, αvβ3 and α5β1 integrins are often upregulated on both tumor cells and on the endothelial cells that mediate tumor angiogenesis to enable tumor growth and dissemination [32–34]. Work targeting vascular integrins as cancer therapy remains unsuccessful due to some combination of low efficacy and side effects [35]. Again, drug development requires balancing integrin roles in these pathological processes with beneficial roles in vascular homeostasis.

Arguably the most straightforward condition in which integrins are a primary target is thrombosis. Blood platelets that mediate clotting are unique in expressing integrin αIIbβ3. Under normal circumstances, platelets integrins are inactive, allowing platelets to circulate freely. Upon vascular injury, activation of the clotting cascade triggers signals within platelets that result in conformational activation of integrin αIIbβ3 to increase its affinity for fibrinogen/fibrin and other ligands, promoting platelet aggregation and thus clotting at the wound site [36]. Platelets also show partial activation in inflammatory environments, which increases their propensity for thrombosis [37]. αIIbβ3 antagonists have thus been developed to inhibit pathological thrombosis, though are used with great care to avoid bleeding complications [38].

Thus, while integrins' essentiality makes them attractive therapeutic targets, their physiological roles place severe constraints. Precise and proper regulation of hemostasis and immunity is required for health. Additionally, vascular homeostasis is an ongoing process. As tissues grow, undergo changes in metabolism or age, demand for vascularization changes. Enabling the circulation to meet tissue metabolic requirements requires its ongoing adaptation via physiological angiogenesis and arteriogenesis. Inadequate vascularity (vascular rarefaction) in aging is a major cause of heart failure, frailty, and other problems [39]. Precision, cautious and careful evaluation of on-target but unwanted effects is thus required.

2. Current Methods of Targeting Integrins and Their Pathways

Currently marketed therapies are mainly small molecules or monoclonal antibodies (Table 1) that bind integrin extracellular domains to block function by occluding the ligand binding site or by preventing conformational conversion to the high affinity state. The main strategy for the first generation of integrin therapies was to target integrins that were both upregulated in disease and had a relatively limited expression profile. Notable examples include αIIbβ3 that is specific to platelets, α4β1, α4β7 and αLβ2 that are specific to immune cells, and αvβ3 on endothelial cells and tumor cells. However, even with these cell type-limited integrins, complications can arise from on-target but harmful effects in other cell types/tissue locations.

Table 1. FDA-approved integrin-targeting therapies.

Category	Therapy Name	Integrin Target	Medical Use	Clinical Phase	Description	Ref
Antibody	Natalizumab (Tysabri)	α4β1 α4β7	Treating Multiple Sclerosis (MS)	FDA approved (2004, 2007), in-use	Prevents inflammatory cells from crossing the blood brain barrier and entering the brain, resulting in immunosuppression within the CNS.	[40,41]
	Abciximab (ReoPro)	αIIbβ3 αvβ3	Reducing risk of thrombosis during surgery	FDA approved (1994), in-use	blocks integrins on the surface of platelets, preventing platelet aggregation and reducing the risk of thrombosis. Commonly used in the treatment of acute coronary syndromes.	[42]
Agonistic Ligand mimetics	7HP349	α4β1 (VLA-4), αLβ2 (LFA-1)	Vaccine adjuvant, treating metastatic melanoma	FDA Fast Track Status (2022)	Small molecule binding activates VLA-4 and LFA-1 on leukocytes, increasing their adhesiveness to promote VLA-4/VCAM-1- and LFA-1/ICAM-1-mediated adhesion between naive T cells and antigen presenting cells (APCs) and enhance T-cell activation.	[35,43]
Adjacent Pathway	Letrozole	αvβ3	Infertility	FDA approved for the treatment of breast cancer (1998), in-use	non-steroidal type II aromatase that inhibits CYP19A1, preventing conversion of androgens to estrogen, thereby reducing uterine weight and elevated leuteinizing hormone. While not approved for infertility specifically, it has been used by physicians for decades to boost IVF effectiveness.	[44,45]
Closed-stabilizing Conformational modifiers	tirofiban	αIIbβ3	Thrombosis inhibitor	FDA approved (1999), in-use	Small molecule inhibitor that inhibits ADP- and collagen-induced platelet aggregation.	[46]
	eptifibatide	αIIbβ3	Thrombosis inhibitor	FDA approved (1998), in-use	binds to the platelet integrin αIIb/IIIa of human platelets and inhibits platelet aggregation.	[47]

Use of the α4 monoclonal antibody (mAb) Natalizumab, approved by the FDA in 2004 for treatment of Multiple Sclerosis (MS), illustrates this complexity. Natalizumab was approved after clinical trials demonstrated an unprecedented 63% reduction in relapse [40,41]. However, it was voluntarily pulled from the market only 1 year later following reports of rare but higher occurrence of progressive multifocal leukoencephalopathy (PML), a devastating viral infection of the white matter of the brain that targets

oligodendrocytes [40, 48]. Patients, however, petitioned to have it restored, leading to its reapproval in 2007, in part because no comparably effective options were available. It was later found that up to 95% of PML cases occur in patients with a pre-disposing immunodeficiency disorders, such as MS, HIV or hematologic malignancies, and was more frequent in patients on previously available immunosuppressants before starting Natalizumab and in patients taking Natalizumab long-term [49,50]. Recent retrospective studies of the Austrian MS Treatment Registry (AMSTR), founded in 2006, followed Natalizumab patients over a 10 year period [50,51]. In one study [51], 15 Natalizumab patients with diagnosed PML were found to have a mortality of 20% compared to 30−50% in non-MS patients and 25.9% in patients with HIV as the cause of immunodeficiency [52]. While survival is increased relative to non-MS patients, the infection also accelerated MS progression. The Expanded Disability Status Scale (EDSS) increased from 3.5 at pre-PML to 6.5 at the last assessment, leading many patients to require mobility assistance [51]. Furthermore, patients recovered from PML were more likely to convert to progressive MS within three years from PML and the EDSS further increased. In fact, this issue is so prevalent in the treatment of MS that in [50] the authors discovered 53.7% of the patients who discontinued Natalizumab treatment cited either fear of PML or PML diagnosis as the reason for stopping treatment. However, while Natalizumab was the first therapy to be linked to PML, it now appears to be a general consequence of immune suppression [49]. This story serves as both a cautionary tale and a source of hope for future integrin therapies since it indicates that the target integrin may still be feasible if risks of PML can be ameliorated, which would benefit all of the at-risk populations [53].

The αIIbβ3 antagonists Eptifibatide and Tirofiban demonstrate progress toward this goal. These are highly potent anti-thrombotic agents [47,54]. Along with ReoPro, their use is limited to IV administration at low doses and in patients without bleeding complications, precautions necessary due to the potential for bleeding [42, 46]. Comparative clinical studies between Eptifibatide and Tirofiban yielded mixed results, although Eptifibatide appeared to offer better safety [55–57]. To look more closely into their mechanisms of action, crystallography and structural studies were done, which distinguished between agonistic compounds that stabilize open, active states and antagonistic compounds that stabilize closed, low-affinity states, providing insights into their mechanisms of action [58]. Both compounds halt the transition from bent-closed to open integrin states, thus, Tirofiban and Eptifibatide are considered closed-stabilizing agents; the detailed molecular mechanism is reported to be by binding a water molecule and preventing its expulsion from the ligand binding site during activation [58,59]. This effect is attributed to polar motifs within their structures, particularly piperazine or piperidine, which hydrogen-bond with water [58]. The precise location of these motifs is critical to their function, highlighting potential avenues for therapeutic development targeting RGD-containing integrins. However, challenges persist regarding systemic off-target effects and the role of metal ions like Mg^{2+} and Mn^{2+} in ligand binding, again necessitating further exploration in integrin therapy development.

Table 2. Ongoing clinical trials on integrin-modulating therapies.

Integrin	Clinical Trial Number	Phase: Status (Estimated Completion)	Pathology	Intervention	Intervention type
α4β7	NCT05611671	Phase 2: Recruiting (2025)	IBD, ulcerative colitis	MORF-057	Ligand mimetic
	NCT05291689	Phase 2: active (2025)			
	NCT04064697	Phase 3: Recruiting (2025)	Ulcerative Colitis (UC) with tissue CytoMegaloVirus (CMV)	vedolizumab	Monoclonal antibody
	NCT02768532	Phase 4: Terminated (2023)	Crohn's Disease		
αvβ8	NCT04152018	Phase 1: Active (2024)	Solid tumors	PF-06940434	Ligand mimetic
αIIbβ3	NCT04284995	Phase 2: Completed (2020)	STEMI	RUC-4 (Zalunfiban)	Ligand mimetic
	NCT04825743	Phase 3: recruiting (2024)			
α2	NCT05024994	Phase 2: Active (2024)	AML, MDS, CMML	E7820	mRNA inhibitor

3. Clinical Trials Using Integrin Therapies

With these recent advances in integrin structural biology, our understanding of the how small molecules modulate integrin function has expanded to the point that this information can be harnessed to modify existing compounds, generate new ones, or screen currently approved compounds for potential integrin-modifying actions. One significant issue for long term use of integrin targeting compounds is the potential to induce neoepitopes that trigger immune recognition and autoimmunity [60], limiting the time that a patient can stay on the medication. Indeed, new small molecule integrin β3 antagonists have been developed that exhibit increased specificity and potency without exposing neoepitopes [61,62]. RUC-1 and its more potent derivatives RUC-2 and -4 inhibit ligand binding, platelet aggregation and in vivo thrombus formation without inducing integrin conformational changes and accompanying neoepitopes. RUC-4 is currently in clinical trials for the treatment of ST-elevation myocardial infarction (STEMI; NCT04825743). Efficient function blocking without the risk of autoimmunity would be a significant step in integrin-therapy safety that would substantially expand their use.

Along these same lines are a class of drugs known as small-molecule protein ligand interface stabilizers (SPLINTS) [63]. Unlike integrins bound to inhibitors that stabilize the closed or open conformations, SPLITS work intercellularly by stabilizing protein-protein interactions (PPIs), limiting neoepitope formation. A novel SPLINT, E7820, is an aromatic sulphonamide that readily crosses the plasma membrane and triggers degradation of integrin α2 mRNA to inhibit tumor angiogenesis [64, 65]. It works as a "molecular glue", stabilizing a complex between an mRNA splicing co-factor, activator of activating protein 1 and oestrogen receptors (CAPERα) with DDB-1 and cullin-4 associated factor 15 (DCAF15). This complex mediates proteasomal degradation of CAPERα. Through a mechanism yet to be elucidated, the inhibition of this splicing factor prevents the translation of α2 mRNA [63].

Another anti-cancer compound, PF-06940434, targeting αvβ8 is also in development. Among the αv integrins, αvβ8 contains an RGD sequence that seems to prefer latent TGFβ complexes in the ECM [66]. Binding of αvβ8 to TGFβ latent complexes triggers force-dependent release of active TGFβ, a potent cytokine with pleiotropic actions in angiogenesis, cancer growth, tissue repair and fibrosis, and immune suppression [43]. TGFβ signaling is altered in many solid tumors to increase tumor growth [66]. However, global inhibition of TGFβ is not feasible due to serious side effects such as widespread immune activation [43]. Targeting this integrin as a means to inhibit TGFβ activation in a limited way in specific settings may therefore be a useful treatment for cancers or other diseases.

Many of the above-mentioned integrin inhibitors were developed as angiogenesis inhibitors. However, integrin-based anti-angiogenesis clinical trials have been unsuccessful [35]. Importantly, these variable or poor outcomes were not necessarily due to poor inhibition of blood vessel growth but to the difficulty of targeting a disease that can evolve to evade therapy. Angiogenesis inhibitors are problematic because they increase tumor hypoxia, which drives tumor evolution toward more aggressive states [67]. However, angiogenesis inhibitors have more recently been paired with other classes of drugs or radiotherapy. This approach was tested with E7820 for treatment of colorectal cancer, combining it with chemotherapy regimen FOLFIRI (NCT01347645, NCT01133990) or cetuximab (NCT00309179). In ongoing cancer clinical trials using E7820, researchers changed gears from solid-tumor cancers (such as colorectal cancer) to blood and bone marrow cancers such as Acute Myeloid Leukemia (AML), Myelodysplastic Syndrome (MDS) and Chronic myelomonocytic leukemia (CMML) (NCT05024994).

Based on the relative success of therapies such as Natalizumab and 7HP349 that target integrins with greater cell-type specific expression, MORF-057 and vedolizumab are being tested for their efficacy in treating Crohn's Disease, ulcerative colitis and inflammatory bowel disease (IBD) by targeting α4β7, which is expressed at high levels in memory T cells [68]. However, based on potential complications from brain infection as shown with Natalizumab, safety studies should be followed very closely for other inhibitors of this integrin. Therefore, while short-term safety studies may pass these compounds for clinical use, their long-term can reveal detrimental effects that limit their use.

4. Taking Integrins out of the Picture: Targeting Their Pathways

An alternative approach for targeting integrin functions avoids the intricacies of integrin structure by

blocking downstream pathways. For example, phosphodiesterase 4D (PDE4D) binds to and is downstream of integrin α5β1 where it makes an important contribution to vascular inflammation and atherosclerosis [13]. Importantly, the PDE family, specifically PDE3, PDE4 and PDE5, has already been successfully targeted for treatment of other diseases such as erectile dysfunction (PDE5; avanafil, sildenafil, tadalafil, vardenafil), Benign prostatic hyperplasia (PDE5; tadalafil), Pulmonary arterial hypertension (PDE5; sildenafil, tadalafil), Psoriatic arthritis (PDE4; apremilast), Psoriasis (PDE4, apremilast), and cardiovascular disease (reviewed in Bondarev 2022) [69]. Inhibitors of PDE4D may therefore have potential in cardiovascular diseases as a means of blocking integrin-dependent pro-inflammatory signaling without affecting the integrins themselves.

There is also interest in the interplay between integrins and G protein-coupled receptors (GPCRs), driven by the prospect of repurposing the large catalogue of approved GPCR therapies as integrin-targeted treatments. This approach is based on recent work in which selectively inhibiting G protein pathways inhibited integrin outside-in signaling while leaving inside-out signaling intact, i.e., blocking signals without blocking cell adhesion [38,70]. These studies demonstrated a direct link between integrin αIIbβ3 activation and Gα13 activation and showed that blocking this interaction reduced thrombosis in animal models [38,70], suggesting a novel approach to thrombotic disorders.

5. Paths forward in Integrin Therapy

The search for better integrin therapies revolves around the search for higher specificity, based mainly on deeper understanding of integrin structural dynamics. Different integrin pairs assume different resting conformations and variable pathways of activation and ligand binding. For example, 8 of the 24 integrins including αvβ3, αvβ5, αvβ6, αvβ8, α5β1, and αIIbβ3 bind RGD peptides, the structure of the RGD-integrin complexes are quite different depending on the receiving MIDAS binding pocket [71] (reviewed in [72]). Furthermore, conformational dynamics for different integrin dimers depend on numerous factors such as the composition of the ECM and extra- and intra-cellular ligands, which vary depending on biological context. *In vitro* systems replicate these complex contexts relatively poorly. Differences in the ECM, in expression of intracellular adapters and regulators, and cell state can affect responses to integrin targeting drugs [35]. For example, the αvβ3 antagonists Etaracizumab and VPI-2690B [73,74] had strong effects in cell culture systems but stalled in phase 2 clinical trials for failing to lead to clinically meaningful reductions in fibrosis in both several kinds of cancers and in kidney disease [73]. Better in vitro systems such as 3D spheroids and engineered tissue models may offer a path to improved drug development [75–79].

Potential off-target and on-target but undesirable effects are major limitations. αv integrins, the most commonly targeted family, are upregulated in cancer and inflammation but still have physiological functions. These integrins play a role in homeostatic vascular remodeling and in bone homeostasis, being constitutively expressed in osteoclasts [80]. One approach to these problems currently under intense development is local delivery. This has been done in mice by implanting biosponges soaked in the αv antagonist IDL-2965 to prevent local muscle fibrosis during regeneration [81]. Specific lipid carriers can target vascular endothelium [82] and hepatocytes [83]. But a good deal of improvement will be required before these approaches gain widespread use in patients. The α5β1 antagonist AXT107 was attached to microparticles for slow release after injection into the eye (NCT05859776) [84–86]. Drug-eluting stents inserted into blocked arteries are widely used in the clinic for coronary and periphery artery disease [87,88]; integrin-targeting compounds might be locally delivered via this route as well [89]. However, even in the wall of an atherosclerotic artery, the same integrin can trigger opposite responses depending on the cell type. Integrin αvβ3 is proinflammatory in endothelial cells but promotes the beneficial contractile phenotype in smooth muscle cells [16, 90, 91]. In endothelial and smooth muscle cells, αvβ3 also promotes migration, which contributes to pathological angiogenesis and atherosclerosis, but has beneficial effects in macrophages/monocytes [92].

Finally, targeting the integrin before it reaches the cell surface may provide a new avenue of drug discovery. For instance, PROTAC (Proteolysis-Targeting Chimeras) technology leverages cell-specific E3 ligases to degrade specific proteins (NCT05573555) [93,94]. This approach could be used in atherosclerosis by exploiting endothelial E3 ligases like HECW2 to target integrins within ECs. There are ongoing clinical trials and studies exploring the applications of PROTAC technology. Combining PROTAC with drug-diffusing stents could improve specific delivery to areas and cells within the vasculature. Alternative

PROTACs are being explored that target proteins at the plasma membrane (PM). These approaches offer the potential for localized control over protein degradation and signaling, which could modulate the complex processes in specific cells or locations. However, it is critical to note that inhibiting integrin αvβ3 with small molecules or antibodies gave virtually opposite results compared to genetic ablation. Inhibitors substantially slowed angiogenesis, while genetic deletion aggressively promoted it [95, 96]. While it is unknown if this phenomenon will repeat with other integrins, it's important to keep in mind if PROTAC technology continues to progress. Interestingly, these studies also evaluated and validated the potential for targeting integrin cytoplasmic tails by showing that point mutations in the β3 tail inhibited tumor angiogenesis, again essentially opposite from the effect of β3-knockout in mice [96–98].

6. Conclusions

The future of integrin-directed therapies lies in improving specificity. Such improvements may be made by targeting pathways of integrin activation to develop inhibitors that avoid neoepitopes, by developing methods to target specific cell types or tissues, or by targeting downstream pathways that show more restricted expression/utilization. The very broad importance of integrins in biological and pathological processes supports their great potential as therapeutic targets, reviewed in [35,38,72]. But the limited number of approved compounds to date underscores the need for a deeper understanding of underlying issues, such as target specificity and conformation. Thus, advances in drug delivery and PROTAC development combined with deeper understanding of integrin structural biology and signaling defines the path forward.

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