## Phylogeny

ACVRL1 (ALK1) belongs to the TGF-β receptor subfamily within the tyrosine-kinase-like (TKL) group of the human kinome, a placement assigned in kinome‐wide classifications referenced by subsequent structural studies (townson2012specificityandstructure pages 13-14, nemec2024discoveryoftwo pages 25-26).  
Orthologs with conserved vascular phenotypes are documented in Mus musculus (Acvrl1) and Danio rerio (acvrl1) knockout models that recapitulate arteriovenous malformations (bernabeu2020potentialsecondhitsin pages 14-16, roman2017alk1signalingin pages 1-2).  
Additional vertebrate orthologs are reported in Gallus gallus and Xenopus laevis based on cross-species sequence analyses within the same publications (roman2017alk1signalingin pages 4-5).  
The closest human paralogues are ALK2/ACVR1 and ALK3/BMPR1A, reflecting conserved GS domains and kinase subdomain architecture across the activin receptor-like kinase family (ornati2014acvrl1(activina pages 2-4, nemec2024discoveryoftwo pages 28-28).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-P (roman2017alk1signalingin pages 4-5).

## Cofactor Requirements

Catalytic activity requires divalent cations; Mg²⁺ is used in kinase and crystallographic assays, and Mn²⁺ can substitute in vitro (nemec2024discoveryoftwo pages 28-28, townson2012specificityandstructure pages 13-14).

## Substrate Specificity

ALK1 phosphorylates the C-terminal SSXS motif of receptor-regulated SMADs (SMAD1, SMAD5, SMAD8), which is the dominant experimentally confirmed consensus sequence for this kinase (roman2017alk1signalingin pages 4-5, nemec2024discoveryoftwo pages 1-3, townson2012specificityandstructure pages 13-14).  
No broader sequence preference beyond this canonical motif is reported in current substrate-profiling datasets cited in the literature (nemec2024discoveryoftwo pages 3-4).

## Structure

The 503-residue single-pass transmembrane receptor comprises:  
• Extracellular domain (ECD, residues 1-118) adopting a three-finger toxin fold that confers ligand selectivity; key interface residues include Arg67, Glu75 and Asn96 (ornati2014acvrl1(activina pages 1-2, townson2012specificityandstructure pages 10-11).  
• Transmembrane helix (residues 119-141) anchoring the receptor (ornati2014acvrl1(activina pages 1-2).  
• GS regulatory domain (residues 180-210) that binds FKBP12 in the inactive state and hosts activating phosphorylation sites Thr204 and Ser206 (townson2012specificityandstructure pages 13-14).  
• Bilobal serine/threonine kinase domain (residues 211-503) solved at 2.1–2.5 Å resolution (PDB 3MY0, 3HMM), displaying a canonical N-lobe β-sheet, a well-positioned αC-helix, intact hydrophobic regulatory spine and a DFG-in activation loop (nemec2024discoveryoftwo pages 25-26).  
The ECD ternary complex with BMP9 and ActRIIB (PDB 4FAO, 2.3 Å) reveals a ligand-induced heterotetramer without major conformational change in the receptor, rationalising its high affinity and specificity (townson2012specificityandstructure pages 10-11).  
An AlphaFold model extends unresolved juxtamembrane regions and supports a flexible linker connecting ECD and kinase core (roman2017alk1signalingin pages 18-19).

## Regulation

Type II receptors ACVR2A, ACVR2B and BMPR2 trans-phosphorylate GS-domain residues Thr204 and Ser206, enabling subsequent ALK1 autophosphorylation within the activation loop and full catalytic activation (townson2012specificityandstructure pages 13-14, nemec2024discoveryoftwo pages 3-4).  
FKBP12 binds the unphosphorylated GS domain and sterically blocks substrate access, acting as an allosteric suppressor (townson2012specificityandstructure pages 13-14).  
The E3 ubiquitin ligase EDD attaches ubiquitin to cytoplasmic lysines, decreasing plasma-membrane receptor abundance and dampening signalling (ornati2014acvrl1(activina pages 1-2).  
No receptor-specific phosphatases are reported in the referenced literature (nemec2024discoveryoftwo pages 25-26).

## Function

ALK1 expression is highly enriched in arterial endothelial cells and is further detected in lung, placenta and hepatic sinusoidal endothelium (roman2017alk1signalingin pages 1-2, ornati2014acvrl1(activina pages 2-4).  
Physiological ligands BMP9/GDF2 and BMP10 bind ALK1 with picomolar affinity, recruiting two type II receptors to form a heterotetrameric signalling complex (townson2012specificityandstructure pages 1-2, roman2017alk1signalingin pages 4-5).  
Endoglin (ENG) functions as an accessory co-receptor that enhances ligand binding and modulates signal strength (roman2017alk1signalingin pages 4-5, bernabeu2020potentialsecondhitsin pages 14-16).  
Activated ALK1 phosphorylates SMAD1/5/8, which complex with SMAD4 to regulate transcriptional programs governing endothelial proliferation, migration and vascular quiescence (roman2017alk1signalingin pages 12-13).  
Loss of ALK1 elevates endothelial PI3K signalling and provokes arteriovenous malformations in zebrafish and mouse models, demonstrating a critical role in flow-dependent vessel patterning (roman2017alk1signalingin pages 12-13, bernabeu2020potentialsecondhitsin pages 14-16).  
In tumours that escape VEGF blockade, ALK1 provides an alternative angiogenic pathway, making it a target for anti-angiogenic therapy (townson2012specificityandstructure pages 11-12, roman2017alk1signalingin pages 21-22).

## Inhibitors

M4K2234 (Kd ≈ 11 nM) and MU1700 (Kd ≈ 13 nM) are structurally orthogonal ATP-competitive probes with >100-fold kinome selectivity, validated in NanoBRET and cellular SMAD assays (nemec2024discoveryoftwo pages 1-3).  
Early tool inhibitors dorsomorphin and its analogue LDN-193189 inhibit ALK1 but suffer from broad off-target activity across the kinome (nemec2024discoveryoftwo pages 28-28).  
Saracatinib, a clinical Src inhibitor, shows sub-micromolar potency against ALK1/ALK2 and has been repurposed for BMP-related disorders (nemec2024discoveryoftwo pages 28-28).  
Biologic antagonists include the soluble receptor trap dalantercept (ALK1-Fc) and the monoclonal antibody PF-03446962, both developed to sequester BMP9/10 and attenuate ALK1 signalling (ornati2014acvrl1(activina pages 7-8, roman2017alk1signalingin pages 21-22).

## Other Comments

Heterozygous loss-of-function mutations in ACVRL1 cause hereditary haemorrhagic telangiectasia type 2 (HHT2), characterised by mucocutaneous telangiectases and arteriovenous malformations (roman2017alk1signalingin pages 4-5, bernabeu2020potentialsecondhitsin pages 14-16).  
Missense variants in the ECD such as H66P, G79R and H87D destabilise disulfide bonding or disrupt BMP9 interface residues, abolishing ligand binding (townson2012specificityandstructure pages 10-11, scotti2011bioinformaticanalysisof pages 1-2).  
Kinase-domain mutations clustering in the C-terminal NANDOR box (codons 479-489) are linked to pulmonary arterial hypertension when co-occurring with HHT (ornati2014acvrl1(activina pages 5-6).  
A pathogenic variant R374Q in the catalytic core reduces SMAD phosphorylation and impairs vascular integrity (nemec2024discoveryoftwo pages 28-28).  
Mouse Acvrl1 null embryos die mid-gestation from cardiac failure and vessel dilatation, underscoring the receptor’s essential developmental role (bernabeu2020potentialsecondhitsin pages 14-16).  
Somatic second-hit mutations are proposed to explain the focal nature of vascular lesions in HHT patients (bernabeu2020potentialsecondhitsin pages 14-16).

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