Narrative Review Article

Recent Advance in Developing Activin-A Receptor Type I Inhibitors for Fibrodysplasia Ossificans Progressiva and Related Disorders

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ABSTRACT

Activin-A receptor type I (ALK2/ACVR1) is a central regulator of bone morphogenetic protein (BMP) signaling, essential for development and tissue homeostasis. The recurrent R206H mutation drives aberrant BMP pathway activation and underlies severe disorders including fibrodysplasia ossificans progressiva (FOP) and diffuse intrinsic pontine glioma (DIPG), with distinct clinical outcomes depending on cellular context. Current therapeutic strategies target mutant ALK2 through ligand-level blockade such as anti–Activin-A antibodies, and direct kinase inhibition using small molecules ranging from early dorsomorphin derivatives to next-generation candidates like BLU-782. Although these approaches have improved potency, significant challenges persist. Emerging structure-guided and allosteric strategies aimed at mutant-selective inhibition offer promising directions. Continued mechanistic and structural characterization of ALK2 mutants will be critical for developing safe, selective and effective therapies. This review aims to summarize recent advances in ALK2-targeted therapeutic strategies and to highlight key challenges and future directions in the development of selective and clinically effective ALK2 inhibitors.

Keywords: ALK2; BMP; Activin-A; FOP; DIPG; Inhibitors; SMAD1/5/8

INTRODUCTION

The Bone Morphogenetic Protein (BMP) signaling pathway is a critical regulator of embryonic development, tissue homeostasis and cellular differentiation. BMP signaling controls diverse biological processes including skeletal patterning, vascular development and stem cell fate determination (1, 2). Because this pathway influences multiple organ systems, its activity must be tightly regulated to maintain physiological balance (3).

Activin-A Receptor Type I (ACVR1), commonly known as ALK2, is a type I BMP receptor that mediates the BMP signaling pathway (4). Upon BMP ligand binding to BMP type II receptors, which form receptor complex with ALK2, and subsequently phosphorylate ALK2, phosphorylated ALK2 then further phosphorylate the downstream SMAD1/5/8 proteins, leading to transcriptional regulation of target genes (5). Through this mechanism, ALK2 contributes to normal skeletal development and tissue repair.

Mutations in the ALK2 gene disrupt regulatory control and lead to pathological activation of BMP signaling. The most common mutation, R206H, accounts for the majority of cases of Fibrodysplasia Ossificans Progressiva (FOP), a rare genetic disorder characterized by progressive heterotopic ossification (6). In addition to

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FOP, somatic ALK2 mutations have been identified in Diffuse Intrinsic Pontine Glioma (DIPG), highlighting the broader pathological significance of dysregulated ALK2 signaling (7). Given the central role of ALK2 in disease pathogenesis, substantial efforts have been directed toward the development of pharmacological inhibitors that suppress abnormal ALK2 receptor activity (8). This article reviews the recent development of ALK2 inhibitors, with a focus on chemical ALK2 inhibitors.

ALK2 MUTATIONS AND DISEASES

Tight spatial and temporal control of BMP signaling is essential for tissue homeostasis, and dysregulation of this pathway, particularly through activating mutations in ALK2, underlies diseases including FOP and Diffuse Intrinsic Pontine Glioma (DIPG) (6, 7, 9). FOP is most commonly caused by a heterozygous ACVR1 c.617G>A (R206H) mutation located in the glycine–serine (GS) regulatory domain of ALK2 (6). Early mechanistic models proposed that this mutation resulted in constitutive hyperactivation of BMP signaling, either through ligand-independent kinase activity or increased sensitivity to BMP ligands, thereby enhancing SMAD1/5/8 phosphorylation and osteogenic gene transcription (10, 11). Structural and biochemical analyses supported the view that disruption of autoinhibitory control within the GS domain destabilized receptor regulation. However, subsequent studies revealed a different mechanism in which Activin-A acts as a pathological agonist of $ALK2^{R206H}$. This is in contrast to the normal function of Activin-A that signals TGF-β pathway via SMAD2/3 and does not activate BMP signaling in wild-type ALK2 (8, 12). In mutant cells containing $ALK2^{R206H}$, Activin-A induces SMAD1/5/8 phosphorylation and drives osteochondral gene programs. Genetic deletion or antibody-mediated inhibition of Activin-A prevents heterotopic ossification in FOP models, establishing Activin-A–dependent signaling as the principal pathogenic driver (8, 12, 13). Thus, FOP is now understood not merely as a disorder of constitutive BMP hyperactivation, but as a Activin-A ligand-dependent signaling reprogramming event. In addition to the R206H mutation, which accounts for more than 95% of FOP cases, several rarer ACVR1 variants have been identified in individuals presenting with either classic or atypical phenotypes. These include mutations R202I, Q207E, R258S, G328E, G328R, G356D and R375P, which similarly enhance SMAD1/5/8 signaling but may be associated with variable clinical severity or atypical skeletal manifestations(14-17). Collectively, these mutations further underscore the critical role of dysregulated ALK2-mediated BMP signaling in the pathogenesis of FOP.

In diffuse midline gliomas, including DIPG, somatic activating ACVR1 mutations occur in approximately 20–30% of tumors and frequently involve residues R206H, G328V and G328E (7, 9). Functional studies demonstrate that these mutations enhance BMP pathway signaling in neural precursor cells (7). Additionally, ALK2 mutations in glioma arise within a neural lineage context commonly characterized by concurrent H3K27M histone mutations (7, 18). The H3K27M mutation results in widespread epigenetic remodeling and altered chromatin accessibility. The combination of enhanced BMP pathway activity and epigenetic dysregulation reprograms transcriptional networks governing proliferation and differentiation, thereby promoting tumorigenesis. These findings illustrate how identical activating mutations in ALK2 can yield divergent pathological outcomes depending on cellular and epigenetic context.

DEVELOPMENT OF ALK2 INHIBITION

Ligand-Level Interventions

As discussed above, Activin-A normally functions within the TGF-β signaling network and does not activate BMP–SMAD1/5/8 signaling through wild-type ALK2 under physiological conditions. In FOP, however, mutations alter ALK2 receptor's function, causing it to respond abnormally to Activin-A and inappropriately activate the bone-forming through BMP-SMAD1/5/8 signaling pathway. This pathological signaling switch induces osteogenic gene expression and is now recognized as a central driver of disease pathogenesis (8, 12). During inflammatory flare-ups or tissue injury, elevated levels of Activin-A further potentiate this abnormal receptor activation, thereby promoting heterotopic ossification (13).

Monoclonal antibodies were developed to neutralize circulating Activin-A, thereby preventing its interaction with mutant ALK2 receptor complexes. The most clinically advanced agent in this category is garetosmab (REGN2477), a fully human monoclonal antibody designed to bind Activin-A with high specificity (19). By neutralizing Activin-A, garetosmab prevents activation of mutant ALK2 and reduces downstream SMAD1/5/8 signaling. In preclinical FOP models, anti–Activin-A antibody treatment significantly suppressed heterotopic ossification formation, supporting the translational

potential of this approach (13). Clinical evaluation progressed to human trials, including the Phase 2 LUMINA-1 study, which demonstrated reductions in new heterotopic bone formation during treatment periods in adults with FOP (19) (NCT03188666). These findings validated the mechanistic hypothesis that blocking Activin-A can attenuate disease activity.

Although Activin-A is a key pathogenic ligand in FOP, mutant ALK2 can still respond to BMP ligands. Therefore, blocking Activin-A alone may not fully eliminate aberrant BMP-SMAD1/5/8 signaling, particularly in inflammatory environments where multiple ligands are present (13, 20). This suggests that ligand-level intervention may provide partial suppression rather than complete pathway normalization. Additionally, Activin-A participates in normal processes including reproductive regulation, immune modulation and tissue repair. Long-term systemic blockade may therefore carry safety implications related to endocrine balance or immune responses (19). Clinical trials have reported adverse events such as mucocutaneous and bleeding-related events, consistent with the broader biological functions of Activin-A.

Another monoclonal antibody under clinical trial is andecaliximab, which targets matrix metalloproteinase-9 (MMP-9), a protease involved in extracellular matrix remodeling and inflammatory tissue responses. During tissue injury and inflammatory flare-ups in FOP, immune cells infiltrate the affected tissue and release enzymes such as MMP-9 that break down the surrounding extracellular matrix. This remodeling process can increase the local release of Activin-A, the key pathogenic ligand in FOP (8, 13, 21). By inhibiting MMP-9 activity, andecaliximab may help reduce inflammatory tissue remodeling and limit Activin-A–driven activation of mutant ALK2-BMP signaling. The drug is being developed by Ashibio Inc. and has previously demonstrated an acceptable safety profile in more than 1,000 patients in clinical studies for other conditions. However, it has not previously been evaluated in individuals with FOP. Andecaliximab is currently being investigated in the clinical trial (NCT06508021), a Phase II/III interventional study designed to evaluate its safety, pharmacokinetics and therapeutic efficacy in both pediatric and adult patients with FOP. The trial was initiated in 2024 and is being conducted at multiple medical centers. Investigators are examining whether treatment with andecaliximab can reduce the frequency and severity of inflammatory flare-ups, limit the development of heterotopic bone lesions, and demonstrate an acceptable safety profile in patients with FOP. Results from this study are expected in 2029.

In summary, ligand-level inhibition of Activin-A represents a rational and clinically advanced therapeutic strategy for FOP. However, neutralization of Activin-A does not fully eliminate aberrant BMP signaling because mutant ALK2 can still respond to BMP ligands. Furthermore, systemic blockade of Activin-A may affect its normal physiological roles in reproduction, immune regulation, and tissue repair. Thus, although anti-Activin-A therapies can reduce pathogenic signaling and new heterotopic ossification, they do not correct the underlying receptor mutation. These limitations highlight the need for complementary approaches, such as mutant-selective ALK2 kinase inhibitors, which directly target the aberrant receptor signaling driving disease progression.

Small-Molecule ALK2 Kinase Inhibitors

In addition to ligand-level interventions, direct inhibition of the mutant ALK2 kinase domain represents another therapeutic strategy for FOP and DIPG. Small-molecule inhibitors have been developed to suppress downstream SMAD1/5/8 signaling at the receptor level (Table 1).

Table 1. *Representative ALK2 inhibitors and their selectivity profiles. Abbreviations: ALK2, activin A receptor type I; ALK1, activin A receptor-like kinase 1; ALK3, activin A receptor type 3; ALK4, activin A receptor type IB; ALK5 activin A receptor type 5; AMPK, AMP-activated protein kinase; VEGFR2, vascular endothelial growth factor receptor 2; RIPK2, receptor-interacting serine/threonine-protein kinase 2; ABL, Abelson tyrosine kinase; WT, wild type; IC_{50}, half-maximal inhibitory concentration.*

Inhibitor	ALK2 (IC_{50})	Selectivity	Major Off-Targets	Ref.
Dorsomorphin (Compound C)	~148 nM	Poor; inhibits multiple BMP type I receptors,	AMPK, VEGFR2	(22)
LDN-193189	~30–40 nM	Moderate selectivity within BMP receptors	VEGFR2, AMPK	(23)

Continued Table 1. *Representative ALK2 inhibitors and their selectivity profiles. Abbreviations: ALK2, activin A receptor type I; ALK1, activin A receptor-like kinase 1; ALK3, activin A receptor type 3; ALK4, activin A receptor type IB; ALK5 activin A receptor type 5; AMPK, AMP-activated protein kinase; VEGFR2, vascular endothelial growth factor receptor 2; RIPK2, receptor-interacting serine/threonine-protein kinase 2; ABL, Abelson tyrosine kinase; WT, wild type; IC_{50}, half-maximal inhibitory concentration.*

Inhibitor	ALK2 (IC_{50})	Selectivity	Major Off-Targets	Ref.
DMH1	~100 nM	Improved selectivity vs ALK4/ALK5	No inhibition to AMPK, VEGFR2	(24)
K02288	~1–2 nM	Potent ALK2 inhibitor but also inhibits ALK1/ALK3	Limited kinase off-targets	(25)
LDN-212854	~1–2 nM	Strong bias toward ALK2 over ALK3/ALK5	Some RIPK2, ABL activity	(26)
ML347	~30 nM	Selective for ALK2/ALK1 over ALK3	Minimal kinase cross-reactivity	(27)
BLU-782	~3–5 nM ($ALK2^{R206H}$)	Slight preference for mutant vs WT ALK2	No reported kinase cross-reactivity	(28)
	~15–25 nM ($ALK2^{WT}$)	Mutant vs WT difference modest		

One of the earliest BMP pathway inhibitors identified was dorsomorphin (compound C), discovered through a zebrafish chemical screen (22). Dorsomorphin inhibits type I BMP receptors including ALK2, thereby reducing SMAD1/5/8 phosphorylation and osteogenic signaling (22) (Figure 1). Although it provided proof-of-concept that pharmacologic inhibition of ALK2 could suppress BMP-driven bone formation, dorsomorphin exhibited significant off-target activity including inhibition of AMP-activated protein kinase (AMPK) and VEGFR2 as well as TGF-β type I receptors such as ALK4 and ALK5, limiting its therapeutic potential (22). Structure–activity optimization led to the development of more potent derivatives such as LDN-193189, which demonstrated improved potency and better inhibition of ALK2 receptors in vitro and in vivo (23) (Figure 1). In preclinical models, LDN-193189 reduced heterotopic ossification and suppressed pathological SMAD1/5/8 signaling associated with FOP mutations(23). Despite these improvements, the compound still exhibits off-target activity against several kinases, including VEGFR2 and AMPK, indicating that further improvements in selectivity were necessary.

Further refinement produced a more selective ALK2 inhibitor, DMH1. DMH1 retains inhibitory activity against ALK2 signaling but shows little or no activity toward several unrelated kinases including VEGFR2 and AMPK(24) (**Figure 1**). It also displays substantially weaker activity against other TGF-β family receptors such as ALK4 and ALK5, indicating improved pathway selectivity compared with earlier compounds. In experimental systems, DMH1 effectively suppressed osteogenic differentiation driven by mutant ALK2 (24). Moreover, additional ATP-competitive inhibitors have been developed to better targ*et al*K2 kinase activity. One example is K02288, a compound identified through structure-guided screening for inhibitors of ALK2 (25) (Figure 1). K02288 exhibits strong inhibitory activity against ALK2 and related BMP receptors and effectively suppresses SMAD1/5/8 phosphorylation in cellular models. However, despite its potent enzymatic activity, K02288 has limited aqueous solubility and suboptimal pharmacokinetic properties, which have restricted its further development as a therapeutic agent (25).

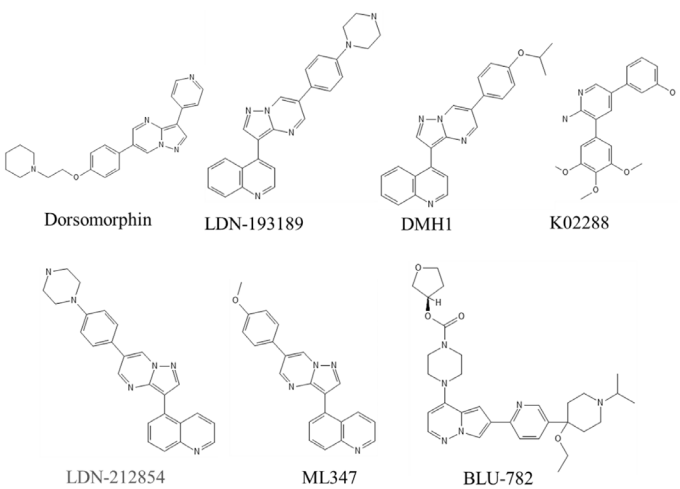

Figure 1. *Chemical Structures of ALK2 inhibitors including Dorsomorphin, LDN-193189, DMH1, K02288, LDN-212854, ML347 and BLU-782.*

More recent medicinal chemistry efforts have focused on developing compounds with improved ALK2 subtype selectivity. One such example is LDN-212854 that was specifically designed to preferentially inhibit ALK2 over other BMP type I receptors, including ALK3 and ALK6. By increasing receptor subtype selectivity, LDN-212854 reduces interference with other signaling pathways within the TGF-β superfamily, thereby potentially improving safety profiles (Figure 1). Preclinical studies have shown that LDN-212854 effectively suppresses BMP signaling and heterotopic ossification in experimental models of FOP (26). Another highly selective chemical probe is ML347, which demonstrates strong inhibitory activity against ALK2 and ALK1 while showing minimal activity against several other kinases (27). Structural and biochemical analyses suggest that ML347 achieves this selectivity through unique interactions within the ATP-binding pocket of the receptor. Although ML347 has primarily been used as a research tool to investigate BMP signaling biology rather than as a therapeutic candidate, it has provided valuable insights into the structural determinants required for selective ALK2 inhibition and has contributed to the rational design of next-generation ALK2 inhibitors (27).

Nevertheless, all the ALK2 inhibitors described above do not distinguish between wild-type and mutant ALK2 receptors. Because FOP arises from a heterozygous ACVR1 mutation, patients retain a functional wild-type allele that is required for normal BMP signaling and tissue homeostasis. Consequently, non-selective inhibition of both receptor forms may disrupt physiological signaling and cause unwanted effects. Therefore, the development of mutant-selective ALK2 inhibitors has become an important goal in FOP drug discovery. More recently, structure-guided drug discovery has led to the development of next-generation ALK2 inhibitors with improved selectivity and drug-like properties. One example is BLU-782, a small-molecule shows greater potency toward mutant ALK2 receptors than toward wild-type ALK2 (28) (Figure 1). Reported inhibitory activity is in the low-nanomolar range for the FOP-associated $ALK2^{R206H}$ mutant ($IC_{50} \approx 3–5$ nM), whereas inhibition of wild-type ALK2 occurs at a concentration ($IC_{50} \approx 15–25$ nM) (Table 1). This differential activity suggests that BLU-782 may preferentially suppress disease-driving signaling while preserving some normal BMP signaling. Preclinical studies have demonstrated that BLU-782 effectively blocks heterotopic ossification in FOP animal models and exhibits improved selectivity compared with earlier BMP pathway inhibitors. Based on these promising findings, BLU-782 has advanced into clinical trials for the treatment of FOP.

Overall, the development of ALK2 inhibitors has progressed from early broad-spectrum BMP inhibitors to compounds with greater potency and improved selectivity for the $ALK2^{R206H}$ mutant. However, even next-generation candidates such as BLU-782, which were designed to preferentially inhibit mutant ALK2 signaling, show only modest differences in potency between mutant and wild-type receptors, indicating that achieving true mutant-specific inhibition remains challenging. Continued efforts to develop highly selective ALK2 inhibitors, particularly those that exploit structural differences in disease-associated receptor conformations, may ultimately lead to safer and more effective therapies for patients with FOP and related disorders.

Challenges in Developing ALK2 Inhibitors

Although significant progress has been made in understanding ALK2 biology and developing small-molecule ALK2 inhibitors, important challenges remain. In particular, achieving high ALK2 kinase selectivity and mutation-specific targeting continues to limit the development of safe and effective ALK2-directed therapies.

One major obstacle is off-target activity. ALK2 shares a highly conserved ATP-binding pocket with other type I receptors including ALK subtypes (ALK1, ALK3, ALK4, ALK5 and ALK6) and the related kinases such as AMPK and VEGFR2. Because of this structural similarity, many ALK2 inhibitors display inhibitory activities against those kinases. For example, dorsomorphin, the first ALK2 inhibitor, also inhibits AMPK and VEGFR2, leading to significant off-target effects (22, 24). Its derivative, LDN-193189, improves potency but still shows off-target activity against ALK3 and other kinases(23). Similarly, K02288 inhibits ALK2 but also targets ALK1 and ALK6, and even more selective compounds such as LDN-212854 do not completely eliminate cross-reactivity, particularly at higher concentrations (25, 29). Among these, off-target inhibition of ALK5 is especially concerning, as disruption of TGF-β signaling has been associated with cardiac toxicity (30). Together, these examples highlight how difficult it is to achieve high selectivity within these closely related kinase receptor families.

A second major challenge is the limited ability to distinguish between wild-type ALK2 and disease-associated ALK2 mutants. As aforementioned, FOP and DIPG are driven by heterozygous ALK2 mutations,

in which mutant and wild-type ALK2 alleles are co-expressed within the same cells. While the mutant ALK2 receptor mediates pathological signaling, the wild-type ALK2 receptor retains its essential role in physiological BMP signaling. This physiological signaling is critical for maintaining normal biological processes including skeletal development, tissue repair, and cellular homeostasis. However, most current inhibitors target the conserved ATP-binding site and therefore inhibit both mutant and wild-type ALK2 with similar potency. This lack of specificity raises an important concern: therapeutic inhibition may inadvertently suppress normal BMP signaling mediated by the wild-type ALK2 allele, potentially leading to adverse effects and narrowing the therapeutic window. Encouragingly, some next-generation compounds have shown modest preference for mutant ALK2, suggesting that mutation-selective inhibition may be achievable. For example, BLU-782 has been designed to enhance selectivity toward mutant ALK2 receptors over the wild-type ALK2 (28). Despite these advances, the development of mutant-selective ALK2 inhibitors remains a significant unresolved challenge. Non-selective inhibition of both mutant and wild-type ALK2 has the potential to disrupt physiological BMP signaling, thereby affecting critical biological processes. Overcoming this limitation will likely require continued advances in structure-based drug design aimed at exploiting subtle structural and conformational differences between mutant and wild-type ALK2. Such advances will be essential to improve therapeutic precision while minimizing off-target effects and preserving normal physiological function.

CONCLUSION

ALK2 is a critical regulator of BMP signaling, and its dysregulation drives the pathogenesis of multiple severe diseases including FOP and DIPG. Although these conditions arise in distinct biological contexts, they share a common mechanism of aberrant ALK2-mediated BMP signaling, making ALK2 an important therapeutic target.

Substantial progress has been made in developing strategies to inhibit ALK2 signaling; however, significant challenges remain in achieving safe and effective clinical translation. These include off-target kinase inhibition, limited selectivity between mutant and wild-type ALK2, and the difficulty of preserving physiological BMP signaling, which is essential for normal development, tissue repair and homeostasis. Current approaches, such as ligand-level blockade of Activin-A and small-molecule kinase inhibitors, have demonstrated therapeutic potential, but remain incomplete due to limited selectivity and possible systemic effects.

Emerging strategies, including structure-guided drug design and allosteric or mutant-selective inhibition, offer promising avenues to improve therapeutic precision. In parallel, overcoming barriers such as central nervous system penetration will be particularly important for treating DIPG. A deeper understanding of ALK2 mutation–specific signaling and structural dynamics will be essential to guide next-generation drug development. Ultimately, achieving selective suppression of pathogenic signaling while preserving normal physiological function will define the success of future therapies for ALK2-driven diseases.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this work.

REFERENCES

1. Hogan BL. Bone morphogenetic proteins: multifunctional regulators of vertebrate development. *Genes Dev.* 1996; 10 (13): 1580-94. https://doi.org/10.1101/gad.10.13.1580
2. Miyazono K, Kamiya Y, Morikawa M. Bone morphogenetic protein receptors and signal transduction. *J Biochem*. 2010; 147 (1): 35-51. https://doi.org/10.1093/jb/mvp148
3. Wu M, Chen G, Li YP. TGF-beta and BMP signaling in osteoblast, skeletal development, and bone formation, homeostasis and disease. *Bone Res*. 2016; 4: 16009. https://doi.org/10.1038/boneres.2016.9
4. ten Dijke P, Yamashita H, Sampath TK, Reddi AH, Estevez M, Riddle DL, *et al*. Identification of type I receptors for osteogenic protein-1 and bone morphogenetic protein-4. *J Biol Chem*. 1994; 269 (25): 16985-8. https://doi.org/10.1016/S0021-9258(17)32506-1
5. Shi Y, Massague J. Mechanisms of TGF-beta signaling from cell membrane to the nucleus. *Cell*. 2003; 113 (6): 685-700. https://doi.org/10.1016/S0092-8674(03)00432-X
6. Shore EM, Xu M, Feldman GJ, Fenstermacher DA, Cho TJ, Choi IH, *et al*. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. *Nat Genet*. 2006; 38 (5): 525-7. https://doi.org/10.1038/ng1783
7. Taylor KR, Mackay A, Truffaux N, Butterfield Y, Morozova O, Philippe C, *et al*. Recurrent activating

ACVR1 mutations in diffuse intrinsic pontine glioma. *Nat Genet*. 2014; 46 (5): 457-61. https://doi.org/10.1038/ng.2925

8. Hatsell SJ, Idone V, Wolken DM, Huang L, Kim HJ, Wang L, *et al*. ACVR1R206H receptor mutation causes fibrodysplasia ossificans progressiva by imparting responsiveness to activin A. *Sci Transl Med*. 2015; 7 (303): 303ra137. https://doi.org/10.1126/scitranslmed.aac4358
9. Wu G, Broniscer A, McEachron TA, Lu C, Paugh BS, Becksfort J, *et al*. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat Genet*. 2012; 44 (3): 251-3. https://doi.org/10.1038/ng.1102
10. Chaikuad A, Alfano I, Kerr G, Sanvitale CE, Boergermann JH, Triffitt JT, *et al*. Structure of the bone morphogenetic protein receptor ALK2 and implications for fibrodysplasia ossificans progressiva. *J Biol Chem*. 2012; 287 (44): 36990-8. https://doi.org/10.1074/jbc.M112.365932
11. Fukuda T, Kohda M, Kanomata K, Nojima J, Nakamura A, Kamizono J, *et al*. Constitutively activated ALK2 and increased SMAD1/5 cooperatively induce bone morphogenetic protein signaling in fibrodysplasia ossificans progressiva. *J Biol Chem*. 2009; 284 (11): 7149-56. https://doi.org/10.1074/jbc.M801681200
12. Hino K, Ikeya M, Horigome K, Matsumoto Y, Ebise H, Nishio M, *et al*. Neofunction of ACVR1 in fibrodysplasia ossificans progressiva. *Proc Natl Acad Sci U S A*. 2015; 112 (50): 15438-43. https://doi.org/10.1073/pnas.1510540112
13. Lees-Shepard JB, Yamamoto M, Biswas AA, Stoessel SJ, Nicholas SE, Cogswell CA, *et al*. Activin-dependent signaling in fibro/adipogenic progenitors causes fibrodysplasia ossificans progressiva. *Nat Commun*. 2018; 9 (1): 471. https://doi.org/10.1038/s41467-018-02872-2
14. Bocciardi R, Bordo D, Di Duca M, Di Rocco M, Ravazzolo R. Mutational analysis of the ACVR1 gene in Italian patients affected with fibrodysplasia ossificans progressiva: confirmations and advancements. *Eur J Hum Genet.* 2009; 17 (3): 311-8. https://doi.org/10.1038/ejhg.2008.178
15. Fiori JL, Billings PC, de la Pena LS, Kaplan FS, Shore EM. Dysregulation of the BMP-p38 MAPK signaling pathway in cells from patients with fibrodysplasia ossificans progressiva (FOP). *J Bone Miner Res*. 2006; 21 (6): 902-9. https://doi.org/10.1359/jbmr.060215
16. Kaplan FS, Xu M, Seemann P, Connor JM, Glaser DL, Carroll L, *et al*. Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. *Hum Mutat*. 2009; 30 (3): 379-90. https://doi.org/10.1002/humu.20868
17. Petrie KA, Lee WH, Bullock AN, Pointon JJ, Smith R, Russell RG, *et al*. Novel mutations in ACVR1 result in atypical features in two fibrodysplasia ossificans progressiva patients. *PLoS One*. 2009; 4 (3): e5005. https://doi.org/10.1371/journal.pone.0005005
18. Chan KM, Fang D, Gan H, Hashizume R, Yu C, Schroeder M, *et al*. The histone H3.3K27M mutation in pediatric glioma reprograms H3K27 methylation and gene expression. *Genes Dev*. 2013; 27 (9): 985-90. https://doi.org/10.1101/gad.217778.113
19. Di Rocco M, Forleo-Neto E, Pignolo RJ, Keen R, Orcel P, Funck-Brentano T, *et al*. Garetosmab in fibrodysplasia ossificans progressiva: a randomized, double-blind, placebo-controlled phase 2 trial. *Nat Med*. 2023; 29 (10): 2615-24. https://doi.org/10.1038/s41591-023-02561-8
20. Aykul S, Corpina RA, Goebel EJ, Cunanan CJ, Dimitriou A, Kim HJ, *et al*. Activin A forms a non-signaling complex with ACVR1 and type II Activin/BMP receptors via its finger 2 tip loop. *Elife*. 2020; 9. https://doi.org/10.7554/eLife.54582
21. Nissinen L, Kahari VM. Matrix metalloproteinases in inflammation. *Biochim Biophys Acta*. 2014; 1840 (8): 2571-80. https://doi.org/10.1016/j.bbagen.2014.03.007
22. Yu PB, Hong CC, Sachidanandan C, Babitt JL, Deng DY, Hoyng SA, *et al*. Dorsomorphin inhibits BMP signals required for embryogenesis and iron metabolism. *Nat Chem Biol*. 2008; 4 (1): 33-41. https://doi.org/10.1038/nchembio.2007.54
23. Cuny GD, Yu PB, Laha JK, Xing X, Liu JF, Lai CS, *et al*. Structure-activity relationship study of bone morphogenetic protein (BMP) signaling inhibitors. *Bioorg Med Chem Lett*. 2008; 18 (15): 4388-92. https://doi.org/10.1016/j.bmcl.2008.06.052
24. Hao J, Ho JN, Lewis JA, Karim KA, Daniels RN, Gentry PR, *et al*. In vivo structure-activity relationship study of dorsomorphin analogues identifies selective VEGF and BMP inhibitors. *ACS Chem Biol*. 2010; 5 (2): 245-53. https://doi.org/10.1021/cb9002865
25. Mohedas AH, Wang Y, Sanvitale CE, Canning P, Choi S, Xing X, *et al*. Structure-activity relationship of 3,5-diaryl-2-aminopyridine ALK2 inhibitors reveals unaltered binding affinity for fibrodysplasia ossificans progressiva causing mutants. *J Med Chem*. 2014; 57 (19): 7900-15. https://doi.org/10.1021/jm501177w
26. Mohedas AH, Xing X, Armstrong KA, Bullock AN, Cuny GD, Yu PB. Development of an ALK2-biased BMP type I receptor kinase inhibitor. *ACS Chem Biol*. 2013; 8 (6): 1291-302. https://doi.org/10.1021/cb300655w
27. Engers DW, Frist AY, Lindsley CW, Hong CC, Hopkins CR. Synthesis and structure-activity

relationships of a novel and selective bone morphogenetic protein receptor (BMP) inhibitor derived from the pyrazolo[1.5-a]pyrimidine scaffold of dorsomorphin: the discovery of ML347 as an ALK2 versus ALK3 selective MLPCN probe. *Bioorg Med Chem Lett*. 2013; 23 (11): 3248-52. https://doi.org/10.1016/j.bmcl.2013.03.113

28. Davis AJ, Brooijmans N, Brubaker JD, Stevison F, LaBranche TP, Albayya F, *et al*. An ALK2 inhibitor, BLU-782, prevents heterotopic ossification in a mouse model of fibrodysplasia ossificans progressiva. *Science Translational Medicine*. 2024; 16 (749). https://doi.org/10.1126/scitranslmed.abp8334
29. Sanvitale CE, Kerr G, Chaikuad A, Ramel MC, Mohedas AH, Reichert S, *et al*. A new class of small molecule inhibitor of BMP signaling. *PLoS One*. 2013; 8 (4): e62721. https://doi.org/10.1371/journal.pone.0062721
30. Azhar M, Schultz Jel J, Grupp I, Dorn GW, 2nd, Meneton P, Molin DG, *et al*. Transforming growth factor beta in cardiovascular development and function. *Cytokine Growth Factor Rev*. 2003; 14 (5): 391-407. https://doi.org/10.1016/S1359-6101(03)00044-3