Recent progress in drug development for fibrodysplasia ossificans progressiva

Xinmiao Meng1 · Haotian Wang2 · Jijun Hao3

Received: 13 January 2022 / Accepted: 8 April 2022 / Published online: 10 May 2022
© The Author(s) 2022

Abstract

Fibrodysplasia Ossificans Progressiva (FOP) is a rare genetic disease caused by heterozygous missense mutations in Activin A receptor type I which is also known as Activin-like kinase 2 (ALK2), a type I receptor of Bone Morphogenetic Proteins (BMP). Patients with FOP usually undergo episodic flare-ups and the heterotopic ossification in soft and connective tissues. Molecular mechanism study indicates that Activin A, the ligand which normally transduces Transforming Growth Factor Beta signaling, abnormally activates BMP signaling through ALK2 mutants in FOP, leading to heterotopic bone formation. To date, effective therapies to FOP are unavailable. However, significant advances have recently been made in the development of FOP drugs. In this article, we review the recent advances in understanding the FOP mechanism and drug development, with a focus on the small-molecular and antibody drugs currently in the clinical trials for FOP treatment.

Keywords Fibrodysplasia ossificans progressiva · ACVR1 · BMP · TGF-β · ALK2 · Heterotopic ossification

Introduction

FOP is a rare human genetic disorder in which ectopic bone formation occurs in connective tissue such as tendons, ligaments, and skeletal muscles throughout the body, leading to progressive loss of mobility, chronic pain, and eventual premature death mainly due to cardiorespiratory failure [1]. A worldwide prevalence of FOP is approximately one in two million population without ethnic, racial, or geographic predisposition [2]. One main symptom of FOP is a malformation of big toes at birth which also serves as an early diagnostic hallmark for FOP [2, 3]. In 2006, the first heterozygous missense causative mutation of FOP (617G>A; R206H) was reported in the gene-encoding ACVR1 [4]. Since then, additional new heterozygous missense causative mutations in ACVR1 have been reported, and further studies indicated that ACVR1R206H mutation occurs in approximately 97% of FOP patients [5, 6] (Fig. 1). ACVR1, also known as ALK2, is a type I receptor of BMP signaling essential for normal skeleton formation and embryonic patterning [7, 8]. For a more complete view of FOP etiology, clinical characteristics, diagnosis, and management, we refer the readers to the excellent reviews in these topics [2, 3, 9].

Early mechanistic studies showed that FOP ALK2 mutants result in leaky BMP signaling in a basal condition and hyper-responsiveness upon BMP ligand stimulation [10–17]. However, recent findings have confirmed that activin A, the ligand which normally transduces TGF-β signaling, abnormally activates BMP signaling through FOP-mutated ALK2 [18–21]. This abnormal activin A-induced BMP signaling is thought to trigger heterotopic ossification of connective tissues [22]. To date, although effective therapies for FOP are unavailable, significant advances have been achieved in the development of potential FOP drugs, resulting in several promising therapies currently in clinical trials [23]. In this article, we review the recent progress in FOP mechanism studies and drug development, with a focus on the small-molecular and antibody drugs in the clinical trials for FOP treatment.
BMP signaling and FOP

BMPs are secreted multi-functional growth factors, and they belong to the TGF-β super family. BMPs consist of more than 20 family members which play central roles in regulating cellular morphogenesis, differentiation, proliferation, and apoptosis during embryogenesis and adult homeostasis [24]. The BMPs signal transduction is mainly mediated through the canonic Smads-dependent pathway in which BMPs first bind to a heterotetrametric complex consisting of a type II receptor homodimer and a type I receptor homodimer (Fig. 2). Then the type II receptors phosphorylate and activate the type I receptors, which in turn phosphorate Smad1/5/9 (also known as Smad1/5/8). The phosphorylated Smad1/5/9 subsequently form a complex with Smad4, which then translocates into the nucleus where it binds to BMP response elements and activates transcription of BMPs target genes [24, 25].

Four type I receptors, ALK1, ALK2, ALK3, and ALK6, are able to mediate BMP signaling and malfunctions of these four types I receptors are involved in many diseases including cancer [26, 27]. In FOP, the most common mutation R206H is located at the intracellular glycine-serine-rich (GS) domain of ALK2, where FKBP12 protein (also known as FKBP1A) binds to ALK2 to prevent ALK2 activation in the absence of BMP ligands [12, 15, 16]. ALK2^{R206H} has been shown to induce basal leaky BMP signaling in the absence of BMP ligands and hyper-responsiveness upon BMP ligand stimulation that was initially thought to result in the ectopic endochondral ossification in FOP [15–17, 28]. Later, additional FOP mutations have been identified in both GS domain and kinase domain of ALK2, which are associated with the disease onset ages and the extent of heterotopic ossification [5, 10, 29–32].

Nevertheless, recent findings have proved that activin A, a ligand which normally transduces TGF-β signaling, abnormally activates BMP signaling in FOP [18–21]. In normal physiological conditions, BMPs utilize ALK1/ALK2/ALK3/ALK6 as the type I receptors to activate Smad1/5/9-dependent BMP signaling, while activin A signals through ALK4/ALK7 as the type I receptors for Smad2/3-dependent TGF-β signaling and activin A does not transduce Smad1/5/9-dependent BMP signaling [33] (Fig. 2). However, recent multiple studies have demonstrated that activin A can activate Smad1/5/9-dependent BMP signaling in cells expressing ALK2^{R206H} in vitro and induced heterotopic ossification in a conditional knock-in mouse model of FOP in vivo [18–21, 34, 35]. In addition, this heterotopic ossification in the FOP mouse model can be blocked by the activin A-specific antibodies supporting that activin A cross-signal BMP pathway via mutated FOP ALK2 receptors [18–21]. Advances in understanding of the
Recent drug development for FOP

Based on the molecular mechanism underlying FOP, multiple potential therapeutic targets have been selected for drug development to treat the disease.

Targeting ALK2

Since FOP is caused by the missense mutations of ALK2, ALK2 has been long thought as a potential therapeutic target for FOP and significant efforts have been made to develop ALK2 inhibitors.

Dorsomorphin, the first ALK2 chemical inhibitor, was identified from an in vivo screening of BMP inhibitors using zebrafish embryos [36] (Fig. 3). Unfortunately, Dorsomorphin displays notable off-targets against several other kinases including Vascular Endothelial Growth Factor Receptor 2 (VEGFR2), ALK5, AMP-activated kinase (AMPK) and platelet-derived growth factor receptor β (PDGFRβ) [37]. Meanwhile, another ALK2 inhibitor, LDN-193189, was developed, and it shows better potency and selectivity than Dorsomorphin [39] (Fig. 3). Nevertheless, both DMH1 and LDN-193189 cannot well distinguish ALK2 from other BMP type I receptors (ALK1/3/6) which are essential for development and homeostasis [40–43]. Therefore, developing better ALK2 inhibitor is critical for FOP treatment with minimum side effects. Further investigations discovered more selective ALK2 inhibitors, ML347 and LDN-212854 with negligible inhibitory activities for all other kinases except ALK1 [44, 45] (Fig. 3). Very recently, Ullrich et al. reported a new potent and selective ALK2 inhibitor, compound 23, which displays excellent biochemical and cellular potency, selectivity, and a favorable in vitro profiles for absorption, distribution, metabolism, and excretion [46]. However, none of the above selective ALK2 inhibitors have moved into clinical trials.

Recently, Williams et al. screened over 220 small-molecular kinase inhibitors which have either been approved previously by FDA or in clinical trials [47]. They identified a potent and selective ALK2 inhibitor, Saracatinib (also known as AZD0530), an orally bioavailable drug developed by AstraZeneca for the treatment of ovarian adenocarcinoma.
Since Saracatinib effectively blocks heterotopic ossification in preclinical FOP models and displays excellent pharmacokinetic parameters and safety, Phase II clinical trial of Saracatinib for FOP was recently initiated in August 2020 (NCT04307953) [49, 50] (Table 1). Another selective ALK2 inhibitor, INCB000928 that was originally developed to treat anemia as an iron homeostasis modulator, is now being evaluated for the efficacy and tolerability in the treatment of FOP in the phase II clinical trial (NCT05090891) [51, 52] (Table 1). Other than small-molecular ALK2 inhibitors, an anti-ALK2 monoclonal antibody, DS-6016a, was developed as well by Daiichi Sankyo and Saitama Medical University in Japan. The Phase I clinical trial of DS-6016a to assess its safety, tolerability, and

![Chemical Structures of Small-Molecular Inhibitors of ALK2, Rapamycin, and Palovarotene](image.png)

**Table 1** Recent clinical trials for FOP (by November 2021).

| Drug name               | Clinical phase | Target      | NCT/UMIN number     |
|------------------------|----------------|-------------|---------------------|
| Saracatinib            | Phase II       | ACVR1       | NCT04307953         |
| INCB000928             | Phase II       | ACVR1       | NCT05090891         |
| DS-6016a               | Phase I        | ACVR1       | NCT0481398          |
| BLU-782 (IPN60130)     | Phase I        | ACVR1       | NCT03858075         |
| REGN2477 (Garetosmab)  | Phase II       | Activin A   | NCT03188666         |
| Rapamycin              | Phase II/III   | mTORC1      | UMIN000028429       |
| Palovarotene           | Phase III      | Nuclear     | NCT03312634         |
|                        |                | RARγ        | NCT05027802         |

*NCT* the national clinical trial, *UMIN* university hospital medical information network
pharmacokinetics in healthy participants is ongoing, and the study results have not been released to date (NCT04818398) [53] (Table 1).

Nevertheless, these ALK2-targeting potential drugs indiscriminately target both wild-type ALK2 and FOP-mutated ALK2, leading to inhibition of important physiologic BMP signaling essential for normal cellular and tissue function. To overcome this challenge, Blueprint Medicines, Inc. developed a small molecule called BLU-782 (also known as IPN60130), which selectively targets the FOP-mutated ALK2 with minimal interference to the wild-type ALK2 [54] (Fig. 3). The Phase I clinical trial BLU-782 in healthy volunteers to establish its safety of the investigational drug was recently completed (NCT03858075), and the result showed that BLU-782 is well tolerated with approximately 24 h of half-life and displays excellent properties of pharmacokinetics and pharmacodynamics [55, 56] (Table 1).

**Targeting activin A**

Activin A normally mediates TGF-β signaling by using Activin Receptors type IIA or IIB (ActR-IIA/ActR-IIB) as type II receptors and ALK4/7 as type I receptors followed by the downstream-phosphorylated Smad2/3 as intracellular signal transducers (Fig. 2). However, recent studies have confirmed that activin A abnormally activates BMP-Smad1/5/9 signaling through mutant ALK2 in FOP [18–21, 34, 35]. Given this interesting discovery, activin A has become a promising therapeutic target for FOP treatment. REGN2477 (also known as Garetosmab), a human anti-activin A-neutralizing antibody, was examined in the FOP mouse model, and the result showed that REGN2477 effectively inhibited heterotopic ossification [19]. The Phase I clinical trial of REGN2477 was completed, and the result demonstrated that REGN2477 displays great safety, tolerability, and pharmacokinetics [57]. Recently its Phase II clinical trial was initiated with a plan to administer 10 mg/kg REGN2477 intravenously every 4 weeks to FOP patients with classic FOP-ALK2R206H mutation and demonstrated that palovarotene (also known as R667), a specific agonist of the retinoic acid signaling by targeting nuclear retinoic acid receptor-γ (RARγ) with well characterized safety profile, inhibited heterotopic ossification in a transgenic mouse model expressing ALK2Q207D mutation [72] (Fig. 3). Later, Chakkalakal et al. examined palovarotene in a knock-in mouse model carrying the classic FOP-ALK2R206H mutation and demonstrated that palovarotene effectively blocks trauma-induced and spontaneous heterotopic ossification without comprising limb mobility and growth [73]. Importantly, palovarotene maintained joint, limb, and body motion, providing clear evidence for its encompassing therapeutic potential as a treatment for FOP [73]. In 2014, Clementia Pharmaceuticals initiated a double-blinded, placebo-controlled Phase II clinical trial to evaluate whether palovarotene prevents heterotopic ossification in FOP.

**Rapamycin**

Rapamycin (also known as Sirolimus) is an immunosuppressive drug used to prevent transplant rejection and lymphangiomiomyomatosis, and it has been recently identified as a potential drug for the treatment of FOP (Fig. 3). In a high-throughput screening by using FOP patient-derived induced pluripotent stem cells (FOP-iPSCs) to identify signaling pathways involved in activin A-induced chondrogenesis, Hino et al. found that the mammalian target of rapamycin (mTOR) signaling is critical in enhanced chondrogenesis initiated by activin A and heterotopic ossification in FOP [66]. They further showed that Rapamycin attenuated heterotopic ossification in both FOP-ALK2R206H conditional transgenic mice and the mice with activin A-triggered heterotopic ossification derived from FOP-iPSCs [66]. Given the promising preclinical studies and its proved safety profile, Phase II/III clinical trials of Rapamycin for randomized, placebo-controlled studies and subsequent open-label extension studies were initiated at Kyoto University Hospital in Japan (UMIN000028429), and the outcomes of this trial has not been publicly released (Table 1). Nevertheless, a case report recently showed that Rapamycin did not show clear benefits to heterotopic ossification reduction in two young patients with classic FOP-ALK2R206H mutation and demonstrated that palovarotene effectively blocks trauma-induced and spontaneous heterotopic ossification in both FOP-ALK2R206H conditional transgenic mice and the mice with activin A-triggered heterotopic ossification derived from FOP-iPSCs [66].

**Palovarotene**

Retinoid signaling mediated by nuclear retinoic acid receptors (RAR) plays a critical biological role in chondrogenesis and normal skeleton formation and retinoic acid signaling agonists could effectively block chondrogenesis and subsequent heterotopic ossification in FOP [68–71]. In 2011, Shimono et al. showed that palovarotene (also known as R667), a specific agonist of the retinoic acid signaling by targeting nuclear retinoic acid receptor-γ (RARγ) with well characterized safety profile, inhibited heterotopic ossification in a transgenic mouse model expressing ALK2Q207D mutation [72] (Fig. 3). Later, Chakkalakal et al. examined palovarotene in a knock-in mouse model carrying the classic FOP-ALK2R206H mutation and demonstrated that palovarotene effectively blocks trauma-induced and spontaneous heterotopic ossification without comprising limb mobility and growth [73]. Importantly, palovarotene maintained joint, limb, and body motion, providing clear evidence for its encompassing therapeutic potential as a treatment for FOP [73]. In 2014, Clementia Pharmaceuticals initiated a double-blinded, placebo-controlled Phase II clinical trial to evaluate whether palovarotene prevents heterotopic ossification in FOP.

**Targeting other associated transcriptional effectors**

It is believed that activin A induces chondrogenesis via BMP signaling in FOP by differentiating connective tissue progenitor cells into chondrocytes and osteoblasts prior to eventual formation of heterotopic bones in soft tissues [34, 65]. Thus, inhibition of chronogenesis may be a good strategy to prevent heterotopic ossification in FOP.
ossification during and following a flare-up in FOP patients (NCT02190747). The trial was completed in 2016, and the result shows that palovarotene reduces the percentage of FOP patients developing heterotopic ossification, the time to remission and patient-reported pain associated with the flare-up area [74]. Currently, the Phase III clinical trial of palovarotene in FOP patients is in progress (NCT03312634). In addition, the rollover Phase III study was launched in November 2021 to further evaluate the safety and efficacy of palovarotene in adult and pediatric participants with FOP who have previously received palovarotene treatment (NCT05027802) [75] (Table 1).

Conclusion

In recent years, significant progresses have been made in understanding the molecular mechanism underlying FOP and developing FOP therapies. The discovery of causative mutations in ALK2 has made it a promising druggable target for FOP. Numerous small-molecular inhibitors and antibodies targeting ALK2 have been developed. Among them, Saracatinib, DS-6016a, and BLU-782 are currently in FOP clinical trials. In addition, as activin A abnormally transduces BMP signaling in FOP, REGN2477 antibody-targeting activin A has been studied for the treatment of FOP, and its efficacy is currently under evaluation in a Phase II clinical trial. Moreover, potential drugs targeting transcriptional effectors associated with the early heterotopic ossification have also shown promise in the treatment of FOP, and their efficacies are being evaluated in clinical trials. For instance, a Phase II clinical trial has showed that RARγ agonist Palovarotene effectively reduces the percentage of FOP patients developing heterotopic ossification and the time to remission (NCT02190747) [74]. Additionally, Rapamycin was shown to attenuate heterotopic ossification in FOP mouse models [66], and a Phase II clinical trial for Rapamycin is currently ongoing. In summary, rapid, and exciting advances have been made in our understanding of FOP mechanism and drug development. Several potential drugs are currently under clinical trials to treat FOP at multiple targets, which allows more effective combinational pharmacological management for FOP. Nevertheless, as physiological BMP signaling is critical to homeostasis and indiscriminately blocking BMP signaling to treat FOP may raise some concerns, therapeutic agents like BLU-782 that selectively targets only the mutant ALK2 with minimal interference to the wild-type ALK2 may represent an excellent strategy for FOP treatment in the future.

Author contributions XM and HW reviewed articles, prepared figures, and wrote original draft. JH supervised the review, organized the figures, wrote, and edited the manuscript. All authors contributed to the critical reading and writing of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability Not applicable.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This is a review article, and no ethical approval is required.

Consent for publication Its publication has been approved by all co-authors.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Kaplan FS, Shen Q, Losnev V, Seemann P, Groppe J, Katagiri T et al (2008) Skeletal metamorphosis in fibrodysplasia ossificans progressiva (FOP). J Bone Miner Metab 26(6):521–530
2. Pignolo RJ, Shore EM, Kaplan FS (2013) Fibrodysplasia ossificans progressiva: diagnosis, management, and therapeutic horizons. Pediatr Endocrinol Rev 10(Suppl 2):437–448
3. Kaplan FS, Xu M, Glaser DL, Collins F, Connor M, Kitterman J et al (2008) Early diagnosis of fibrodysplasia ossificans progressiva. Pediatrics 121(5):e1295–e1300
4. Shore EM, Xu M, Feldman GJ, Fenstermacher DA, Cho TJ, Choi IH et al (2006) A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet 38(5):525–527
5. Furuya H, Ikezoe K, Wang L, Ohyagi Y, Motomura K, Fujii N et al (2008) A unique case of fibrodysplasia ossificans progressiva with an ACVR1 mutation, G356D, other than the common mutation (R206H). Am J Med Genet A 146A:459–463
6. Kaplan FS, Groppe JC, Xu M, Towler OW, Grunvald E, Kalunian K et al (2022) An ACVR1(R375P) pathogenic variant in two families with mild fibrodysplasia ossificans progressiva. Am J Med Genet Part A 188(3):806–817
7. Huse M, Muir TW, Xu L, Chen YG, Kuriyan J, Massague J (2001) The TGF beta receptor activation process: an inhibitor- to substrate-binding switch. Mol Cell 8(3):671–682

Author contributions XM and HW reviewed articles, prepared figures, and wrote original draft. JH supervised the review, organized the
8. Huse M, Chen YG, Massague J, Kuriyan J (1999) Crystal structure of the cytoplasmic domain of the type I TGFbeta receptor in complex with FKB P12. Cell 96(3):425–436
9. Haga N, Nakashima Y, Kitoh H, Kamizono J, Katagiri T, Saijo H et al (2020) Fibrodysplasia ossificans progressiva: review and research activities in Japan. Pediatr Int 62(1):3–13
10. Kaplan FS, Xu M, Seemann P, Connor JM, Glaser DL, Carroll L et al (2009) Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. Hum Mutat 30(3):379–390
11. Groppe JC, Shore EM, Kaplan FS (2007) Functional Modeling of the ACVR1 (R206H) mutation in FOP. Clin Orthop Relat Res 462:87–92
12. Groppe JC, Wu J, Shore EM, Kaplan FS (2011) In vitro analyses of the dysregulated R206H ALK2 kinase-FKB P12 interaction associated with heterotopic ossification in FOP. Cells Tissues Organs 194(2–4):291–295
13. Chaikuad A, Alfano I, Kerr G, Sanvitale CE, Boergermann JH, Triffitt JT et al (2012) Structure of the bone morphogenic protein receptor ALK2 and implications for fibrodysplasia ossificans progressiva. J Biol Chem 287(44):36990–36998
14. Bagarova J, Vonner AJ, Armstrong KA, Borgermann J, Lai CS, Deng DY et al (2013) Constitutively active ALK2 receptor mutants require type II receptor cooperation. Mol Cell 53(12):2413–2424
15. Shen Q, Little SC, Xu MQ, Haupt J, Ast C, Katagiri T et al (2009) The fibrodysplasia ossificans progressiva R206H ACVR1 mutation activates BMP-independent chondrogenesis and zebrafish embryo ventralization. J Clin Invest 119(11):3462–3472
16. Song GA, Kim HJ, Woo KM, Baek JH, Kim GS, Choi JY et al (2010) Molecular consequences of the ACVR1(R206H) mutation of fibrodysplasia ossificans progressiva. J Biol Chem 285(29):22542–22553
17. van Dinther M, Visser N, de Gorter DJ, Doorn J, Goumans MJ, de Boer J et al (2010) ALK2 R206H mutation linked to fibrodysplasia ossificans progressiva confers constitutive activity to the BMP type I receptor and sensitizes mesenchymal cells to BMP-induced osteoblast differentiation and bone formation. J Bone Miner Res 25(6):1208–1215
18. Hino K, Ikeya M, Horigome K, Matsumoto Y, Ebise H, Nishio M et al (2015) Neofunction of ACVR1 in fibrodysplasia ossificans progressiva. Proc Natl Acad Sci USA 112(50):15438–15443
19. Hatsell SJ, Idone V, Wolken DM, Huang L, Kim HJ, Wang L et al (2015) ACVR1R206H receptor mutation causes fibrodysplasia ossificans progressiva by imparting responsiveness to activin A. Sci Transl Med. https://doi.org/10.1126/scitranslmed.aac4358
20. Olsen OE, Wader KF, Hella H, Mylin AK, Turesson I, Nes-thus I et al (2015) Activin A inhibits BMP-signaling by binding ACVR2A and ACVR2B. Cell Commun Signal 13:27
21. Upadhyay J, Xie L, Huang L, Das N, Stewart RC, Lyon MC et al (2017) The expansion of heterotropic bone in fibrodysplasia ossificans progressiva is activin A-dependent. J Bone Miner Res. https://doi.org/10.1002/jbmr.3235
22. Alessi Wolken DM, Idone V, Hatsell SJ, Yu PB, Economides AN (2018) The obligatory role of Activin A in the formation of heterotropic bone in fibrodysplasia ossificans progressiva. Bone 109:210–217
23. Connor JM, Woodrow JC, Evans DAP (1982) Histocompatibility antigens in patients with ectopic ossification due to fibrodysplasia ossificans progressiva. Ann Rheum Dis 41(6):646–647
24. Bragdon B, Moseychuk O, Saldanha S, King D, Julian J, Nohe A (2011) Bone morphogenetic proteins: a critical review. Cell Signal 23(4):609–620
25. Sanchez-Duffues G, Williams E, Goumans MJ, Heldin CH, Ten Dijke P (2020) Bone morphogenetic protein receptors: structure, function and targeting by selective small molecule kinase inhibitors. Bone 138:115472
26. Loomans HA, Andl CD (2016) Activin receptor-like kinases: a diverse family playing an important role in cancer. Am J Cancer Res 6(11):2431–2447
27. Lin S, Svoboda KK, Feng JQ, Xie Y (2016) The biological function of type I receptors of bone morphogenetic protein in bone. Bone Res 4:16005
28. Botello-Smith WM, Alsamara A, Chatterjee P, Xie C, Lacroix JJ, Hao J et al (2017) Polyomol allostatic regulation of type I serine/threonine kinase receptors via a conserved electrostatic lock. PLoS Comput Biol 13(8):e1005711
29. Whyte MP, Westenfeld RF, Westenfeld ER, Mumm S (2012) Fibrodysplasia ossificans progressiva: middle-age onset of heterotopic ossification from a unique missense mutation (c.974G>C, p.G325A) in ACVR1. J Bone Min Res 27(3):729–737
30. Bocciardi R, Bordo D, Di Duca M, Di Rocco M, Ravazzolo R (2009) Mutational analysis of the ACVR1 gene in Italian patients affected with fibrodysplasia ossificans progressiva: confirmations and advancements. Eur Hum Genet 17(3):311–318
31. Wei X, Duan H, Wang SY, Zhao HL, Liao Y, Li Y et al (2009) Novel mutations in ACVR1 result in atypical features in two fibrodysplasia ossificans progressiva patients. PLoS ONE 4(3):e5005
32. Cappato S, Traberg R, Gintautiene J, Zara F, Bocciardi RA (2021) Case of fibrodysplasia ossificans progressiva associated with a novel variant of the ACVR1 gene. Mol Genet Genomic 9(10):e1774
33. Massague J (2012) TGFβ signalling in context. Nat Rev Mol Cell Biol 13(10):616–630
34. Wang H, Shore EM, Pignolo RJ, Kaplan FS (2018) Activin A amplifies dysregulated BMP signaling and induces chondro-osseous differentiation of primary connective tissue progenitor cells in patients with fibrodysplasia ossificans progressiva (FOP). Bone 109:218–224
35. Xie C, Jiang WJ, Lacroix JJ, Luo Y, Hao JJ (2020) Insight into molecular mechanism for activin A-induced bone morphogenetic protein signaling. Int J Mol Sci 21(18):6498
36. Yu PB, Hong CC, Sachidanandan C, Babitt JL, Deng DY, Hoyng SA et al (2008) Dorosmorhin inhibits BMP signals required for embryogenesis and iron metabolism. Nat Chem Biol 4(1):33–41
37. Hao J, Ho LN, Lewis JA, Karim KA, Daniels RN, Gentry PR et al (2010) In vivo structure-activity relationshipship study of dorosmorphin analogues identifies selective VEGF and BMP inhibitors. ACS Chem Biol 5(2):245–253
38. Luo Y, Alsamara A, Zhang K, Hao J (2016) Development of new therapeutic agents for fibrodysplasia ossificans progressiva. Curr Mol Med 16(1):4–11
39. Cuny TD, Yu PB, Laha JK, Xing X, Lai JS, Lai CS et al (2008) Structure-activity relationshipship study of bone morphogenic protein (BMP) signaling inhibitors. Bioorg Med Chem Lett 18(15):4388–4392
40. Goumans MJ, Valdimarsdottir G, Itoh S, Rosendahl A, Sideras P, ten Dijke P (2002) Balancing the activation state of the bone morphogenetic protein (BMP) signaling inhibitors. Bioorg Med Chem Lett 12(16):2431–2435
41. Hu-Lowe DD, Chen EH, Zhang LL, Watson KD, Mancuso P, Perla A et al (2012) Discovery of a new class of potent BMPR2 antagonists by a high-throughput screen using an in vitro bone assay. J Med Chem 55(2):750–754
42. Chen H, Shibata T, Watanabe M, Mochida E, Shintani M, Nakayama T, Furutani Y, Hayama E, Inai K et al (2012) Missense mutations of the BMPR1B (ALK6RT2) gene.
in childhood idiopathic pulmonary arterial hypertension. Circ J 76(7):1501–1804

43. Cunha SI, Pietras K (2011) ALK1 as an emerging target for antiangiogenic therapy of cancer. Blood 117(26):6999–7006

44. Engers DW, Frist AY, Lindsley CW, Hong CC, Hopkins CR (2013) 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 Dorosomorphin: the discovery of ML347 as an ALK2 versus ALK3 selective MLPCN probe. Bioorganic Med Chem Lett 23(11):3248

45. Mohedas AH, Xing XC, Armstrong KA, Bullock AN, Cuny GD, Yu PB (2013) Development of an ALK2-biased BMP Type I receptor kinase inhibitor. ACS Chem Biol 8(6):1291–1302

46. Ulrich T, Arista L, Weiler S, Teixeira-Fouchard S, Brouennimann V, Stief N et al (2022) Discovery of a novel 2-amino-pyrazine-3-carboxamide as a potent and selective inhibitor of activin receptor-like kinase-2 (ALK2) for the treatment of fibrodysplasia ossificans progressiva. Bioorg Med Chem Lett. https://doi.org/10.1016/j.bmcl.2022.128667

47. Williams E, Bagarova J, Kerr G, Xia DD, Place ES, Dey D et al (2021) Saracatinib is an efficacious clinical candidate for fibrodysplasia ossificans progressiva. JCI Insight. https://doi.org/10.1172/jci.insight.95042

48. Hennesquin LF, Allen J, Breed J, Curwen J, Fennell M, Green TP (2012) Study of single-ascending doses of DS-6016a in healthy Japanese participants With Fibrodysplasia Ossificans Progressiva (2018). https://clinicaltrials.gov/ct2/show/NCT03858075. Accessed 12 Dec 2021

49. Chen YY, Stubbs MC, Pusey M, Wen XM, Collins RJ, Kapilas-Hrami K et al (2020) Characterization of INCB00928, a potent and selective ALK2 inhibitor for the treatment of anemia. Blood 136:52–52

50. To assess the efficacy, safety, and tolerability of INCB00928 in participants With Fibrodysplasia Ossificans Progressiva (2021). https://clinicaltrials.gov/ct2/show/NCT05090891. Accessed 12 Dec 2021

51. Study of single-ascending doses of DS-6016a in healthy Japanese subjects (2021). https://clinicaltrials.gov/ct2/show/NCT04307953. Accessed 12 Dec 2021

52. Blueprint medicines presents foundational preclinical data supporting the development of BLU-782, a highly selective ALK2 inhibitor, for the treatment of patients with fibrodysplasia ossificans progressiva (2016). https://clinicaltrials.gov/ct2/show/NCT03858075. Accessed 14 Dec 2021

53. In childhood idiopathic pulmonary arterial hypertension. Circ J 76(7):1501–1804

54. Allison DFA, Riadh L, Michael P, Cori AS, Sara G, Faith S, Sean V, Stiefl N et al (2022) Pharmacokinetics and pharmacodynamics of garetosmab (Anti-activin A) results from a first-in-human phase 1 study. J Clin Pharmacol 60(11):1424–1431

55. A study to examine the safety, tolerability and effects on abnormal bone formation of REGN2477 in patients with fibrodysplasia ossificans progressiva (2017). https://clinicaltrials.gov/ct2/show/NCT03188666. Accessed 16 Dec 2021

56. N-(5-chloro-1,3-benzodioxol-4-yl)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5- (tetrahydro-2H-pyran-4-yloxy)quinazolin-4-amine, a novel, highly selective, orally available, dual-specific c-Src/Abl kinase inhibitor. J Med Chem 49(22):6465–6488

57. Pacifici M (2018) Retinoid roles and action in skeletal development and growth provide the rationale for an ongoing heterotopic ossification prevention trial. Bone 109:267–275

58. Underhill TM, Cash DE, Linney E (1994) Constitutively active retinoid receptors exhibit interfamily and intrafamily promoter specificity. Mol Endocrinol 8(3):274–285

59. Weston AD, Hoffman LM, Underhill TM (2003) Revisiting the role of retinoid signaling in skeletal development. Birth Defects 39(4):454–460

60. Shimoto K, Tung WE, Macolino C, Chi AH, Didizian JH, Mundy C et al (2011) Potent inhibition of heterotopic ossification by nuclear retinoic acid receptor-gamma agonists. Nat Med 17(4):454–460

61. Hedger MP, Winnall WR (2012) Intra-ovarian roles of activin and inhibin in the human ACVR1(R206H) fibrodysplasia ossificans progressiva. Nat Commun 9(1):471

62. Petrakou E, Fotopoulos S, Anagnostakou M, Anatolitou F, Samitas K, Semitekolou M et al (2013) Activin-A exerts a crucial anti-inflammatory role in neonatal infections. Pediatr Res 74(6):675–681

63. Mayer K, Buchbinder A, Morty RE (2012) Activin A: a mediator governing inflammation, immunity, and repair. Am J Respir Crit Care Med 185(4):350–352

64. Rodriguez-Martinez G, Molina-Hernandez A, Velasco I (2012) Activin A promotes neuronal differentiation of cerebrocortical neural progenitor cells. PLoS ONE 7(8):e43797

65. Kaplan FS, Hsiao EC, Baujat G, Keen R, Grogan DR, Pignolo RS, Cogswell CA et al (2018) Activin-dependent signaling in fibro/adipogenic progenitors causes fibrodysplasia ossificans progressiva. Nat Commun 9(1):471

66. Hino K, Horigome K, Nishio M, Komura S, Nagata S, Zhao C et al (2017) Activin-A enhances mTOR signaling to promote aberrant chondrogenesis in fibrodysplasia ossificans progressiva. J Clin Invest 127(9):3393–3392

67. Kaplan FS, Zeitlin L, Dumn SP, Benor S, Hagan D, Al Mukaddam M et al (2018) Acute and chronic rapamycin use in patients with fibrodysplasia ossificans progressiva: a report of two cases. Bone 109:281–284

68. Pacifici M (2018) Retinoid roles and action in skeletal development and growth provide the rationale for an ongoing heterotopic ossification prevention trial. Bone 109:267–275

69. Weston AD, Rosen V, Chandraratna RA, Underhill TM (2000) Regulation of skeletal progenitor differentiation by the BMP and retinoid signaling pathways. J Cell Biol 148(4):679–690

70. Pacifici M (2018) Retinoid roles and action in skeletal development and growth provide the rationale for an ongoing heterotopic ossification prevention trial. Bone 109:267–275

71. Westphal H, Hoffmann LM, Underhill TM (2003) Revisiting the role of retinoid signaling in skeletal development. Birth Defects 39(4):454–460

72. Shimoto K, Tung WE, Macolino C, Chi AH, Didizian JH, Mundy C et al (2011) Potent inhibition of heterotopic ossification by nuclear retinoic acid receptor-gamma agonists. Nat Med 17(4):454–460

73. Chakkalalak SA, Uchibe K, Convente MR, Zhang D, Economides AN, Kaplan FS et al (2016) palovarotene inhibits heterotopic ossification and maintains limb mobility and growth in mice with the human ACVR1(R206H) fibrodysplasia ossificans progressiva (FOP) Mutation. J Bone Min Res 31(9):1666–1675

74. Kaplan FS, Hsiao EC, Baujat G, Keen R, Grogan DR, Pignolo RS, Cogswell CA et al (2018) Activin-dependent signaling in fibro/adipogenic progenitors causes fibrodysplasia ossificans progressiva. Nat Commun 9(1):471

75. Saracatinib Trial To Prevent FOP (2020). https://clinicaltrials.gov/ct2/show/NCT04307953. Accessed 12 Dec 2021

76. Kaplan FS, Hsiao EC, Baujat G, Keen R, Grogan DR, Pignolo RS, Cogswell CA et al (2018) Activin-A enhances mTOR signaling to promote aberrant chondrogenesis in fibrodysplasia ossificans progressiva. J Clin Invest 127(9):3393–3392

77. Kaplan FS, Zeitlin L, Dumn SP, Benor S, Hagan D, Al Mukaddam M et al (2018) Acute and chronic rapamycin use in patients with fibrodysplasia ossificans progressiva: a report of two cases. Bone 109:281–284

78. Pacifici M (2018) Retinoid roles and action in skeletal development and growth provide the rationale for an ongoing heterotopic ossification prevention trial. Bone 109:267–275

79. Underhill TM, Cash DE, Linney E (1994) Constitutively active retinoid receptors exhibit interfamily and intrafamily promoter specificity. Mol Endocrinol 8(3):274–285

80. Pacifici M (2018) Retinoid roles and action in skeletal development and growth provide the rationale for an ongoing heterotopic ossification prevention trial. Bone 109:267–275

81. Underhill TM, Cash DE, Linney E (1994) Constitutively active retinoid receptors exhibit interfamily and intrafamily promoter specificity. Mol Endocrinol 8(3):274–285