

## Review

## Fibroblast Growth Factor 23 as a Therapeutic Target

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## ABSTRACT

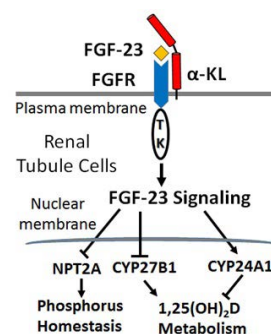
This fibroblast growth factor-23 (FGF-23) has been found as a circulating hormone and pathogenic factor in many disease conditions. This review focuses on recent advances in FGF-23 as a therapeutic target, including fibroblast growth factor receptors (FGFR) tyrosine kinase inhibitor, FGF-23 antibody, FGF-23 C-terminal peptide, *CYP24A1* inhibitor, and FGF-23 antagonist. We also update the advantages and disadvantages of targeting upstream and downstream molecules in FGF-23 signaling pathways.

## INTRODUCTION

Fibroblast growth factor-23 (FGF-23) is a bone-derived hormone that inhibits phosphate reabsorption and 1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D) production by the kidney<sup>1,2</sup> (Figure 1). Physiologically, FGF-23 regulates systemic phosphate homeostasis and vitamin D metabolism through a bone-kidney axis.<sup>3,4</sup> However, excess FGF-23 in genetic disorders leads to hypophosphatemic rickets as well as may play a pathogenic role in adverse outcomes in chronic kidney disease.<sup>5-7</sup> Primary increases in FGF-23 have been reported in rare hereditary hypophosphatemic disorders in humans and their mouse homologues,<sup>8-19</sup> including X-linked hypophosphatemic rickets (XLH)/Hyp mice, caused by inactivating mutations of *Phex*,<sup>14,15,20</sup> autosomal recessive hypophosphatemic rickets 1 (ARHR1), caused by inactivating mutations of *Dmp1*,<sup>15,20</sup> ARHR2, caused by inactivating mutations in *ENPP1*,<sup>10,14-17</sup> and Raine Syndrome (RNS), caused by inactivation mutations in *FAM20C*.<sup>21,22</sup> as well as tumor-induced osteomalacia (TIO).<sup>23-25</sup> Secondary elevations of FGF-23 occurs in chronic kidney disease (CKD).<sup>1,26</sup> Elevated FGF-23 is initially an adaptive response to altered mineral metabolism in chronic kidney disease (CKD)<sup>27</sup>, but chronic elevations of FGF-23 are maladaptive and linked to increased morbidity and mortality,<sup>6</sup> cardiovascular disease,<sup>6,28-31</sup> and inflammation<sup>32,33</sup> in CKD. Therefore, control of FGF-23 levels as well as its upstream and downstream signaling pathways could serve as a potential target to improve outcomes in many disease conditions. Currently, fibroblast growth factor receptors (FGFR) tyrosine kinase inhibitor (NVP-BGJ398),<sup>34,35</sup> *CYP24A1* inhibitor,<sup>36</sup> FGF-23 antibody (KRN23),<sup>37,38</sup> FGF-23C-terminal peptide,<sup>39,40</sup>

and FGF-23 antagonist<sup>41</sup> are being developed to treat disorders of excess FGF-23. This review will summarize recent advances in these areas.

**Figure 1.** FGF-23 Signaling in Renal Tubule Cells. FGF-23, FGFR, and  $\alpha$ -Klotho ( $\alpha$ -KL) form Ternary Complex to Activate FGFR Tyrosine Kinase Activity, Transduce FGF-23 Signaling to Downstream Targeted Genes NPT2A, CYP27B1, and CYP24A1, and Regulate Renal Phosphorus Homeostasis and 1,25(OH)<sub>2</sub>D Metabolism



## FGFR KINASE INHIBITOR

There is compelling evidence to support pharmacological inhibition of FGFRs in excess FGF-23. First, FGF-23 signaling is transduced by members of the FGF receptor (FGFRs, 1, 3, 4) family in conjunction with the essential co-receptor Klotho, which confers tissue-specificity for endocrine FGF-23 signals owing to its

predominant expression in kidney (Figure 1).<sup>42</sup> Second, hereditary hypophosphatemic disorders such as XLH/*Hyp* and ARHR1 involve activation of FGFR signaling and FGF-23 expression in osteocytes<sup>17</sup> and osteocyte-specific deletion of *Fgfr1* in *Hyp* mice markedly suppresses FGF-23 production.<sup>18</sup> Third, a gain-of-function mutation in FGFR1 causes osteoglophonic dysplasia (OGD), which is also associated with hypophosphatemia and elevated FGF-23 levels.<sup>43</sup> Theoretically, it is useful to develop FGFR inhibitors that control FGF-23 signaling and production in disorders of excess FGF-23. In this regard, FGFR tyrosine kinase inhibitor (NVP-BGJ398) has been developed to treat FGF-23-mediated hypophosphatemic diseases and has been shown to block both the production and end-organ effects of FGF-23.<sup>34,35</sup> However, NVP-BGJ398 is a small molecule with potent inhibitory activity of FGFRs 1, 3, and 4 and lacks selectivity for FGF-23/FGFR/ $\alpha$ -KL signaling, and their generalized ability to inhibit FGFRs in multiple tissues would have undesirable effects.<sup>34,35</sup> In addition, a small molecule, SSR128129E (SSR), which binds to the extracellular part of FGFR, was reported to act as a FGFR antagonist.<sup>44,45</sup> So far, SSR128129E are being developed as anti-tumor drugs since these compounds have limitations, including specificity and potential toxicities. At present, there are no small molecules that specifically modulate FGF-23 activation of FGFR/ $\alpha$ -KL complexes. The discovery of such molecules would not only provide research tools to elucidate FGF-23 biological actions, but also would advance the discovery of new treatments based on this novel bone/kidney endocrine network.

### FGF-23 ANTIBODY

A FGF-23 specific antibody [Burosumab, KRN23, Ultragenix (USA) and Kirin (Japan)] has been developed as a therapy for XLH.<sup>37,38,46</sup> KRN23 binds to and inhibits the biological activity of FGF-23. However, loss of FGF-23 function can have serious side effects, including hyperphosphatemia and soft-tissue calcifications. Indeed, preclinical studies in CKD models show that inhibiting FGF-23 with a high affinity blocking antibody increased mortality,<sup>38</sup> leading to no current plans to test KRN23 in CKD. Lowering FGF-23 in CKD is controversial, since use of calcimimetics to suppress PTH leads to modest reductions in FGF-23 and improved survival in patients with end-stage renal disease (ESRD).<sup>47</sup> Since 30 million people or 15% of USA adults are estimated to have CKD and elevated FGF-23,<sup>48</sup> identifying a drug to dose-dependently and reversibly reduce FGF-23 may improve CKD outcomes. To avoid toxicity, a low affinity FGF-23 blocking antibody (KRN23) was selected for clinical development. Clinical trials with KRN23 show efficacy to raise serum phosphate and improve rickets in XLH.<sup>37,38</sup> Although hyperphosphatemia occurred in ~6% of the KRN23 treated XLH patients, biologics such as KRN23 are plagued by high cost, the need for parenteral delivery, long half-life, and difficulty with dose titration. From the business perspective, there is an opportunity to develop a small, orally bioavailable small molecule to inhibit FGF-23.

### FGF-23 C-TERMINAL PEPTIDES

Full-length FGF-23 is a 32-kDa protein that can be cleaved at 176RXXR179 site by a cellular endoprotease furin, leading to the

22-kDa N-terminal and 16-kDa C-terminal fragments.<sup>13</sup> Recent studies have shown that the C-terminal tail of FGF-23 (FGF-23C) can compete with full-length ligand for binding to the FGFR/ $\alpha$ -KL complex, and hence can antagonize the phosphaturic activity of FGF-23 *in vivo*, both in healthy rats and in a mouse model of phosphate wasting disorders.<sup>39,40</sup> In order to increase the half-life of the FGF-23C peptide, the investigators generated a FGF-23C Fc fusion molecule and demonstrated that repeated injection of this molecule (twice a week, 10 mg/kg) selectively modulates the phosphate pathway *via* regulation of *NPT2A* expression *in vivo* by competitive antagonism of FGF-23 binding to the FGFR/ $\alpha$ -KL co-receptor in *Hyp* mice, a preclinical model of XLH. The unique ability of FGF-23C Fc molecule to preferentially modulate the FGFR1/ $\alpha$ -KL phosphate pathway but not FGFR3&4/ $\alpha$ -KL in the control of 1,25(OH)<sub>2</sub>D levels in kidney makes this molecule ideal for use as a new therapeutic in the treatment of XLH, with the potential to significantly improve bone formation in XLH patients with limited safety concerns.<sup>39,40</sup>

### CYP24A1 INHIBITOR

FGF-23 impairs the production of renal 1,25(OH)<sub>2</sub>D through either inhibiting the expression of *CYP27B1*, the enzyme that converts 25-(OH)D to its active metabolite, or upregulating the expression of vitamin D 24-hydroxylase (*CYP24A1*), a mitochondrial enzyme responsible for inactivating vitamin D metabolites through the C-24 oxidation pathway.<sup>49</sup> In the overexpressing mutant FGF23R176Q and *Hyp* mouse models, hypophosphatemic rickets with high levels of FGF-23 are also associated with increased renal *CYP24A1* expression, suggesting that elevated *CYP24A1* activity is pivotal to the pathophysiology of these disorders.<sup>50,51</sup> Knockout of *CYP24A1* in the *Hyp* and FGF23R176Q-transgenic mice resulted in near-complete recovery of rachitic bony abnormalities, but serum levels of phosphorus and 1,25(OH)<sub>2</sub>D did not improve in these murine models of human disease.<sup>36</sup> Interestingly, treatment of *Hyp* and FGF23R176Q-transgenic mice with the *CYP24A1* inhibitor CTA102 also ameliorated their rachitic bones.<sup>36</sup> Whether pharmacologic inhibition of *CYP24A1* activity goes solo as a therapeutic target remains to be further investigated.

### FGF-23 ANTAGONIST

In addition to FGF-23 specific antibody and FGF-23 C peptide, a computationally identified FGF-23 antagonist (ZINC13407541) was found to bind to FGF-23 that disrupts its interaction with the FGFR/ $\alpha$ -KL complex in a heterologous cell expression system.<sup>41</sup> This FGF-23 antagonist was also shown to inhibit FGF-23 signaling in isolated renal tubules *ex vivo* and to increase serum phosphate and 1,25(OH)<sub>2</sub>D in a mouse model of FGF-23-related hypophosphatemic diseases.<sup>41</sup> In addition, this FGF-23 antagonist slightly but significantly reduced FGF-23 levels along with increased PTH levels in mouse disease model.<sup>41</sup> The findings of small molecule that antagonizes FGF-23 activation of FGFRs provide a new tool to probe the functions of FGF-23 and set the stage for developing clinical drug candidates to treat disorders of excess FGF-23. Furthermore FGF-23 antagonist can be cost-effective, orally bioavailable and easily dose titration compared to the FGF-23 antibody. This small molecule has been using to

**Table 1. GrSmall Molecules and Biologics in Treating Disorders of Excess FGF-23**

Reagent	Mechanism of Action	Positive/Negative Aspects	References
FGFR Kinase Inhibitor	Inhibition of FGFR tyrosine kinase	Blocking both the production and end-organ effects of FGF-23/no specificity	34,35
FGF-23 Antibody	Function blocking	High specificity of treatment and dose titratability/Cost and parenteral delivery	37,38
FGF-23 C-terminal Peptides	Competitive antagonism of FGF-23 binding	High specificity of treatment/the increased proteolytic instability during treatment	39,40
CYP24A1 Inhibitor	Inhibition of CYP24A1 activity	Recovery of rachitic bone/no effect on levels of phosphorus and 1,25(OH)2D	36
FGF-23 Antagonist	Disruption of FGF-23 binding to FGFR/ $\alpha$ -KL complex	Orally bioavailable, dose titratability, and cost-effective/Short half-time	41

develop lead compound for preclinical screening and late clinical trials.

#### THE POTENTIAL SIDE EFFECTS OF THESE FGF-23 TARGETED THERAPIES

As shown in Table 1, all of current FGF-23 targeted therapies have their advantages and disadvantages. The FGFR inhibitors show a strong inhibition of FGFR tyrosine kinase activity; these compounds can block both the production and end-organ effects of FGF-23, but demonstrate no specificity and potential tissue and organ toxicity. In contrast, FGF-23 antibody plays a function blocking on FGF-23 and displays a high specificity of treatment. However, FGF-23 antibody needs parenteral delivery and high cost treatment. FGF-23 C-terminal peptides also have a high specificity of treatment, but the increased proteolytic instability during treatment would limit its use as a long-time therapeutic strategy.<sup>52</sup> CYP24A1 inhibitor almost completely recover rachitic bone of hypophosphatemic disorder, but this compound has no effect on levels of phosphorus and 1,25(OH)2D. FGF-23 antagonist could be a promising therapeutic strategy because of effective, orally bioavailable and easily dose titration compared to the FGF-23 antibody. This small molecule has been using to develop lead compound for preclinical screening and late clinical trials.

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strategy.<sup>52</sup> CYP24A1 inhibitor almost completely recover rachitic bone of hypophosphatemic disorder, but this compound has no effect on levels of phosphorus and 1,25(OH)2D. FGF-23 antagonist could be a promising therapeutic strategy because of its oral bioavailability, dose titratability, and cost-effective if the optimization overcomes the short half time of the compound.

#### CONCLUSION

Fibroblast growth factor-23 is a circulating hormone that regulates phosphate and vitamin D metabolism. Excess actions of FGF-23 result in reductions in serum phosphate and 1,25(OH)2D levels and hypophosphatemic disorders. Therefore, it is necessary to develop therapeutic methods to suppress the activities of this hormone. In fact, patients with hypophosphatemic disorders by FGF-23 excess were reported to benefit from FGF-23 blocking antibodies or inhibitors of FGF-23 signaling.<sup>37,53,54</sup> However, these therapies need careful monitoring dosing-use because deficient actions of FGF-23 result in hyperphosphatemic disease.<sup>55,56</sup> Indeed, management of FGF-23 levels in patients with CKD seems to be debatable since modest reductions in FGF-23 with calcimimetics could improve survival in patients with ESRD,<sup>47</sup> while inhibiting FGF-23 with a high affinity blocking antibody increased mortality in CKD,<sup>38</sup> leading to questionable benefit from these novel therapies in CKD. However, use of either low affinity FGF-23 antibody or FGF-23 inhibitors to control FGF-23 excess actions remains a promising therapy for both hereditary and acquired hyperphosphatemic diseases.

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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