

What Should Be Done To Cure Him:

Lightning or the Lightning Bug for Fibrodysplasia Ossificans Progressiva (FOP)?

(an editorial)

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For nearly three centuries, fibrodysplasia ossificans progressiva (FOP), one of the most disabling conditions known to mankind, has seemed to many like a hopeless cause. The childhood victims of this rare musculoskeletal sabotage appear physically normal at birth except for characteristic malformations of the great toes.^{1,2} That is the last time, however, that things appear relatively normal for the world's approximately 700 known individuals with this condition. Soon thereafter, usually between two and five years of age, children with FOP succumb to progressive and episodic waves of inflammation-induced ectopic skeletogenesis that transform the body's soft connective tissues into an armament-like encasement of bone, in effect, a second skeleton.^{1,2} Massive and rapidly-appearing soft-tissue swellings (flare-ups), usually triggered by minimal trauma, are often the first sign of the metamorphosis.³ Ribbons, sheets, and plates of heterotopic bone replace the body's soft connective tissues, span the joints, lock them in place, and relegate its victims to a state of permanent and lifelong immobility. Any attempt to remove this heterotopic bone leads to additional episodes of explosive soft tissue swelling and subsequent new bone growth.² Although corticosteroids may greatly ameliorate symptoms of acute flare-ups, their long-term use in prevention or treatment is questionable.^{2,4}

FOP, known by many names throughout history, was first placed on the medical and scientific agenda by John Freke, a London physician, who wrote to The Royal Society on April 14th, 1736: "There came a boy of healthy look, and about 14 years of age, to ask of us at the hospital, **what should be done to cure him** of many large swellings on his back which began about three years since and have continued to grow as large on many parts

as a penny-loaf, particularly on the left side. They arise from all the vertebrae of the neck and reach down to the os sacrum; they likewise arise from every rib of his body and joining together in all parts of his back, as the ramifications of coral do, they make, as it were, a fixed bony pair of bodice.”⁵

What should be done to cure him? Nearly two centuries later in 1918, Jules Rosenstirn of San Francisco wrote: “One does not wonder that a disease, so baffling in its course from the first causes to its ultimate state, should invite the speculative as well as the patiently investigating observer to lift the obscuring veil and solve this embarrassing puzzle.”⁶

An embarrassing puzzle it remained for nearly another century until early 2006 when the FOP gene was discovered with a liberating wave of hope.⁷ As Ian Cali, a young man with FOP said upon learning of the gene discovery and upon understanding the insight it provided for an eventual treatment and cure, “It is no longer a matter of *if*, but a matter of *when*.”⁸

In reality however, cures for rare genetic diseases are rare occurrences. Shakespeare wrote, “Diseases desperate grown, by desperate appliance are relieved, or not at all.”⁹ But, desperation can give rise to reason, reason to inquiry, inquiry to discovery, and discovery to knowledge. Knowledge is a powerful medicine.

Coincidental discoveries often propel science and medicine in serendipitous and unanticipated ways. The discovery of the FOP gene, coupled with the extraordinary specificity of the causative mutation in a highly conserved bone morphogenetic protein (BMP) receptor, immediately predicted the discovery of known molecules to block it.¹⁰ “With so much being discovered about how the BMPs act,” said Brigid Hogan, a prominent developmental geneticist, nearly a decade earlier in response to emerging discoveries in FOP, “it might be possible to develop drugs that would block some part of the BMP pathway, and therefore prevent the progression of what is a horrible nightmare disease.”^{11,12}

What should be done to cure him? Recently, Charles Hong (and colleagues), working in the field of cardiovascular research, re-discovered a unique signal transduction inhibitor, compound C, that was initially identified as an inhibitor of AMP activated kinase (AMPK) activity.¹³ By screening a large library of chemical compounds for their ability to dorsalize zebrafish embryos and thereby inhibit BMP signaling, Hong discovered that compound C (which he renamed Dorsomorphin) could non-specifically inhibit all BMP type I receptors. Hong also discovered that Dorsomorphin specifically inhibits the Smad limb of the BMP signaling pathway without affecting transforming growth factor-beta (TGF- β) or p38 MAPK activity.¹³ Thus, Dorsomorphin provides a powerful new tool for dissecting the effects of BMP signaling.¹⁴

The recurrent and highly specific mutation in the gene encoding Activin receptor 1A/Activin-like kinase 2 (ACVR1/ALK2) that causes FOP was originally suspected to be

a constitutively active mutation.^{7,15} However, recent studies have shown that while FOP cells exhibit a low level of ligand-independent (constitutive) activity, they also exhibit robust non-constitutive activity in response to ligand.¹⁶⁻¹⁸ These and other FOP studies, conducted collaboratively by scientists at The University of Pennsylvania in Philadelphia (USA), The Max Planck Institute for Molecular Genetics in Berlin (Germany), Harvard University (USA), and Saitama Medical University in Saitama (Japan), show that basally active BMP signaling in FOP cells, mediated through the Smad pathway (but not the p38MAPK pathway which has been associated with the induction of inflammation), can be blocked by Dorsomorphin, the compound recently described by Charles Hong and his colleagues.¹⁵⁻¹⁸ These studies establish the proof-of-principle that promiscuous BMP receptor activity, as in FOP, could be blocked, at least in part, by Dorsomorphin.

What should be done to cure him? In the November 30, 2008 online issue of *Nature Medicine*, in a paper entitled: “BMP Type I Receptor Inhibition Reduces Heterotopic Ossification,” Yu et al. further examine a more selective derivative of Dorsomorphin in an animal model of inflammation-induced heterotopic ossification.¹⁹ In their study, the authors show that a newer, more potent, and slightly more specific derivative of Dorsomorphin (LDN-193189; DM-3189) partially blocks heterotopic ossification caused by an artificially constructed and constitutively active mutation of ACVR1/ALK2 that is conditionally triggered by an inflammatory viral stimulus.^{19,20} Despite the allusions in the abstract, the Dorsomorphin derivative was not tested against the classic FOP mutation in this study nor was it very effective in blocking heterotopic chondrogenesis or ossification induced by the constitutively active mutation. In their study, Yu and

colleagues were not able to accomplish what Noggin, a secreted BMP antagonist, did with similar specificity five years earlier.²¹ Interestingly, the study shows that corticosteroids, a standard symptomatic treatment for early FOP flare-ups, were just as effective as the Dorsomorphin derivative in preventing inflammation-induced heterotopic ossification in their model, albeit with greater systemic side-effects. While the abstract and discussion are overstated regarding both the methods used and the conclusions derived, the authors were able to confirm the recently established principle that an inflammatory stimulus can induce heterotopic ossification in a BMP-conducive environment.^{22,23} They further suggest that the newer Dorsomorphin derivatives might be developed as a treatment for FOP.^{19,24} However, despite their impressive work, the authors do not explicitly acknowledge either the surrogate nature of their FOP model or the fact that not a single FOP patient in the world suffers from the genetic mutation studied in their system.^{25,26}

What should be done to cure him? While the Yu et al. study makes an important contribution towards developing treatments for heterotopic ossification and possibly for FOP, lest we succumb to irrational exuberance, there are important matters to consider and perhaps occasion for pause:

1. Although several animal models [including the one used by Yu et al. (2008b)],²⁰ mimic various clinical and molecular features of FOP, not one of these models reproduces the features of classic FOP, nor the distinct molecular mechanisms of FOP.^{1,2,7,18}

2. The mutation that causes classic FOP is recurrent and highly specific in all affected individuals.^{7,26} Although the constitutively active mutation at codon 207 engineered by Mishina et al. (and used by Yu et al.2008b) has features of FOP-like bone formation, it is not FOP, nor is its molecular mechanism the same.^{7,17,18} There are no known FOP patients in the world who harbor the mutation tested in the present study.²⁶
3. The effects of Dorsomorphin derivatives (regardless of dose) are far more potent and non-specific than simply blocking promiscuous ACVR1/ALK2 activity in FOP. Currently available Dorsomorphin derivatives block all BMP-specific Smad phosphorylation from BMP type I receptors, but not p38 MAPK activity,¹³ a pathway that appears to be relevant to FOP and regulated directly by ACVR1/ALK2.^{16,18,27}
4. In a zebrafish model of classic FOP, Dorsomorphin causes severe lethal embryopathy,¹⁸ and in post-natal mouse studies causes seizure activity (unpublished results), a recently noted and atypical feature of FOP. Whether newer Dorsomorphin derivatives are more specific and less toxic in animal models of classic FOP remains to be tested.
5. Although the highly specific and recurrent mutation in ACVR1 (R206H) that causes FOP in all classically affected individuals exhibits low level basal

constitutive BMP activity through the Smad signaling pathway, the mutant receptor also displays impressive responsiveness to stimulation by BMP ligands and other extracellular mediators through the p38MAPK pathway.^{16,27} This branch of the ACVR1-regulated BMP signaling pathway is completely unresponsive to Dorsomorphin and its derivatives, and does not appear to be relevant to the codon 207 mutation studied by Yu and colleagues. Thus, the model studied by Yu et al.²⁰ may not provide an accurate representation of the ability of Dorsomorphin derivatives to block heterotopic ossification in classic FOP.

6. Only testing in an animal model of classic FOP (presently in progress) will indicate how effective Dorsomorphin derivatives may be in preventing or abrogating the pathologic features of classic FOP, suffered by real FOP patients.²⁵
7. Dorsomorphin and its derivatives are one of several novel therapeutic approaches presently being studied in FOP, based on the recent gene discovery. Others include blocking monoclonal antibodies, BMP antagonists, inhibitory RNA, and agents to alter the intracellular microenvironment of an early FOP flare-up.²⁸ It is still far too early to determine which approach or combination of approaches may be most beneficial to FOP patients. Presently, all are being robustly investigated.

What should be done to cure him? FOP is a catastrophic disease with unimaginable human suffering. Affected patients and their families are vulnerable to hype, and are suspicious of inflated claims. While studies on Dorsomorphin derivatives provide much

hope, much additional work needs to be done before any novel compounds can be brought to the clinic. Dorsomorphin derivatives must be tested for efficacy, not in a surrogate model, but in an animal model of classic FOP, and must be fully vetted for safety in several animal models before testing in humans could be considered. Safety and pharmacokinetic studies are mandatory. Much additional work needs to be done, and is underway.

The literature is filled with examples of promising signal transduction inhibitors that fail in the safety arena because of lack of specificity. Unfortunately, neither Dorsomorphin nor any of its recently synthesized derivatives is specific for the FOP gene and none have been tested in a model of classic FOP. As with Noggin, Dorsomorphin derivatives are non-specific, thus effectively blocking all BMP type I receptors as well as AMP kinase to a lesser degree. Their chronic use, an almost certain necessity for FOP patients, would likely cause toxicity. There is much opportunity here for medicinal chemists and x-ray crystallographers who are already working diligently to solve this important roadblock to chronic therapy. The short-term use of Dorsomorphin derivatives may actually not be necessary, if corticosteroids, as suggested by Yu et al. are equally effective. Possibly, the compounds could be used in tandem or sequentially to lessen mutually exclusive side effects. Of note, in the current treatment of FOP, corticosteroids are routinely used to ameliorate the symptoms of acute FOP flare-ups, and if used early enough in the course of a flare-up, may abrogate symptoms entirely.^{2,4} Further experimentation will help clarify these issues.

Dorsomorphin and its derivatives are not the first treatments to be proposed for FOP, nor will they be the last. As Jules Rosenstirn noted in 1918, “The disease was attacked with all sorts of remedies and alternatives for faulty metabolism; everyone of them with more or less marked success observed solely by its original author, but pronounced a complete failure by every other follower.”⁶

What should be done to cure him? For FOP patients and their families, for whom this work means the most and for whom the most is at stake, there is reason for hope. But, there is also ample reason for reserve. At the very least, Dorsomorphin and its derivatives are powerful new tools to dissect the intricacies of BMP signaling in FOP and in other disorders of dysregulated BMP pathway activity.^{14,24} Dorsomorphin and its derivatives are possibly more, but it is much too early to know.

FOP patients and their families, as with individuals who have any rare and devastating disorder, look for every word of hope. But, the difference between hope and hype is one letter. As FOP patients and their families know from the story of the FOP gene discovery, one letter can change the meaning of a word (especially a genetic word) and that can alter the destiny of a human life.⁷

As Mark Twain wrote in a letter in October 1888, “The difference between the almost right word and the right word is really a large matter – it’s the difference between the lightning bug and lightning.”²⁹ Whether Dorsomorphin derivatives are just lightning bugs or are real lightning is yet to be determined. For the FOP community, the FOP gene

discovery was a lightning strike, as it illuminated the way to the next horizon. If the next generation of Dorsomorphin derivatives, presently being developed by several laboratories, proves to be effective, safe, and specific in animal models of classic FOP, and eventually in patients, it may be a case of lightning striking twice. As John Freke asked nearly three centuries ago after seeing a young man with FOP who sought his help: **“What should be done to cure him?”**⁵ Two hundred seventy-two years later, we still do not have a definitive answer, but at least now, we have some hope and a glimmer of light.

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