

Commentary

Is “CTGF” Still a Viable Anti-Fibrotic Target?

Andrew Leask *

School of Dentistry, University of Saskatchewan, Saskatoon, SK S7H 5E7, Canada

* Corresponding author. E-mail: Anl312@usask.ca (A.L.)

Received: 15 August 2025; Accepted: 23 September 2025; Available online: 24 September 2025

ABSTRACT: Cellular communication network factor 2 (CCN2, formerly known as ‘connective tissue growth factor’ or ‘CTGF’) was the subject of anti-fibrotic drug development programs, largely in FibroGen, starting in the mid-1990s. This led to the development of FG-3019 (pamrevlumab) as a lead drug that was used initially to target diabetic nephropathy and subsequently pancreatic cancer, pulmonary fibrosis and Duchenne’s muscular dystrophy. All these programs failed clinically; diabetes in early development, and the others at Phase III. Could these failures have been anticipated? Is ‘CTGF’ dead as an anti-fibrotic target? What might have been done differently or could be done differently in the future? This personal commentary—based on years of experience first at FibroGen working on the ‘CTGF’ program and then as an independent academic researcher—aims to address at least some of these issues.



© 2025 The authors. This is an open access article under the Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>).

Connective tissue growth factor, or ‘CTGF’, was identified in the early 1990s based on its purported growth factor-like properties [1]. Not long after, ‘CTGF’ was shown to be induced by the potent pro-fibrotic cytokine transforming growth factor-beta (TGFbeta) [2]. Based on these observations, Gary Grotendorst and FibroGen proposed that ‘CTGF’ was a downstream mediator of TGFbeta’s pro-fibrotic effects [3]. One of the target indications was scleroderma [4–6]. At FibroGen, two drug development programs were formed: one aimed at blocking either the action of CTGF through an anti-CTGF antibody, the other aimed at blocking the ability of TGFbeta to induce the CTGF promoter. This led to partnerships with FibroGen, with Taisho and Sankyo, respectively. On one hand, this led to the identification of CTGF as a target gene of the mechanosensitive transcription factor YAP1 and contributed to the overall consensus that an autocrine pro-adhesive signaling loop centered on the YAP/hippo pathway was responsible for fibrosis [7–9]. On the other hand, this led to the development of FG-3019 (pamrevlumab), an anti-CTGF antibody, and multiple failed clinical trials centered on FG-3019 [10,11]. I have reviewed the first topic, pertaining to scleroderma, elsewhere [12]. This present commentary focuses on the second topic, namely the failure of anti-CTGF strategies to work clinically.

The story starts in the late 1990s where it became clear that ‘CTGF’ was not a stand-alone molecule. Instead, based on structural similarity, ‘CTGF’ was a member of what came to be known as the CCN family of matricellular proteins consisting of: CCN1 (cyr61), CCN2 (ctgf), CCN3 (nov) and CCN4-6 (wisp 1-3), which act coordinately [13,14]. These proteins were shown not to have growth factor properties but to be pro-adhesive, based on their abilities to bind a variety of integrins and heparan sulfate proteoglycans. For a summary of these studies, the reader is referred elsewhere [15]. The initial notion that CCN2 was a downstream mediator of the actions of TGFbeta did not have direct evidence when it was initially proposed; rather, CCN2 was shown subsequently by several groups to be a cofactor that augmented the action of TGFbeta *in vitro* and *in vivo* [16,17]. *In vitro*, this activity required the presence of CCN2 in the microenvironment and did not occur in naïve cells [18,19].

Despite these concerns, in the early 2000s, FG-3019 was developed. FG-3019 was selected based on its anti-fibrotic activity in animal models, initially in those relying on the effects of continued applications of exogenously added TGFbeta [20] and subsequently in other models, including those of scleroderma fibrosis [21].

Despite its use in the research community, it is noteworthy that FG-3019 was never been demonstrated to have efficacy in any established *in vitro* assay, including adhesion or TGFbeta synergy assays. Significantly, its anti-fibrotic effects have not been attributed to its ability to bind to and antagonize CCN2. Conversely, gene knockout approaches have been used to show that CCN2 is essential for fibrosis in a variety of animal model systems; these studies have been used as a basis to demonstrate that CCN2 is a bona fide anti-fibrotic target [22–24].

Thus, the failure of an anti-CCN2 drug in the clinic may not relate to the absence of legitimacy of CCN2 as a target (although, please see below), but rather due to issues relating to the drug itself. Crucially, the general absence of published mechanistic studies on FG-3019 makes it difficult to evaluate the drug properly. Notably, sufficient FG-3019 was made available to selected researchers to conduct initial efficacy studies only. However, a key paper published by FibroGen scientists may be insightful [25]. This study showed that FG-3019 is eliminated in the plasma proportionate to the levels of circulating CCN2. The authors state: “In a subject with disease that may be producing and shedding more CTGF, target-mediated elimination would be expected to play a larger role in the clearance of FG-3019....(n)o staining for FG-3019 was seen in the heart and lung of animals treated with FG-3019 only”. These results suggest that FG-3019 poorly penetrates tissue, with circulating CCN2 levels correlating with the degree of fibrosis [23,24]. These data collectively suggest that FG-3019 may inherently be a poor drug. A recent study further emphasized these concerns: FG-3019 showed poor target tissue penetration [26]. Collectively, in addition to speculation that pamrevlumab may have failed due to differences in patient inclusion/exclusion criteria between the Phase II and III idiopathic pulmonary fibrosis (IPF) clinical trials and concerns applicable to IPF trials in general [10,27,28], these results suggest that FG-3019 was simply an suboptimal drug candidate.

Having established that CCN2 is a bona fide anti-fibrotic target and FG-3019 may not have been an ideal drug candidate, where does this leave us? One option would be to use a different anti-CCN2 strategy that better penetrates target tissue [25,26]. Another option is to recall what turned out to be a major mistake: the discoverer and marketer of ‘CTGF’ as an anti-fibrotic target either ignored, or refused to consider, that ‘CTGF’ is a member of a multiprotein family, that have redundant functions (for detailed discussions, including illustrations, of these concepts, please see refs [14,23,24]). Indeed, CCN1 and CCN4 both have, depending on the context, pro-fibrotic roles, including in the lung and in a scleroderma skin model [29–32]. Due to this functional redundancy, drugs targeting CCN2 only may not be effective clinically. FG-3019 was designed based on its ability to target CCN2 alone. Perhaps a superior strategy might be to develop approaches based on other members of the CCN family, such as CCN3, that are anti-fibrotic and would be expected to antagonize all pro-fibrotic CCNs [33,34]. Alternatively, using a combinatorial approach using drugs that target individual CCN proteins may be useful. In any case, mechanistic insights underlying how any future anti-CCN drug works are required. These insights could be gleaned using robust *in vitro* and *in vivo* assays, including modern techniques such as spatial and scRNAseq transcriptomic analyses, and validation with clinical samples are required.

In summary, the failures of FG-3019 in the clinic are not likely to reflect on the suitability of the CCN family—or even CCN2—as an anti-fibrotic target, but rather in the quality of the drug itself, and the lack of insight into how FG-3019 was selected or functions. Thus, future science-based approaches are required to investigate whether anti-CCN drugs can be used clinically to treat fibrosis.

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

No novel data was generated or used in this study.

Funding

AL is funded by the Canadian Institutes of Health Research.

Declaration of Competing Interest

The author was a former employee of FibroGen. The author declares no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Bradham DM, Igarashi A, Potter RL, Grotendorst GR. Connective tissue growth factor: a cysteine-rich mitogen secreted by human vascular endothelial cells is related to the SRC-induced immediate early gene product CEF-10. *J. Cell Biol.* **1991**, *114*, 1285–1294.
2. Igarashi A, Okochi H, Bradham DM, Grotendorst GR. Regulation of connective tissue growth factor gene expression in human skin fibroblasts and during wound repair. *Mol. Biol. Cell* **1993**, *4*, 637–645.
3. Grotendorst GR. Connective tissue growth factor: a mediator of TGF-beta action on fibroblasts. *Cytokine Growth Factor Rev.* **1997**, *8*, 171–179.
4. Igarashi A, Nashiro K, Kikuchi K, Sato S, Ihn H, Grotendorst GR, et al. Significant correlation between connective tissue growth factor gene expression and skin sclerosis in tissue sections from patients with systemic sclerosis. *J. Investig. Dermatol.* **1995**, *105*, 280–284.
5. Shi-wen X, Pennington D, Holmes A, Leask A, Bradham D, Beauchamp JR, et al. Autocrine overexpression of CTGF maintains fibrosis: RDA analysis of fibrosis genes in systemic sclerosis. *Exp. Cell Res.* **2000**, *259*, 213–224.
6. Leask A. Transcriptional profiling of the scleroderma fibroblast reveals a potential role for connective tissue growth factor (CTGF) in pathological fibrosis. *Keio J. Med.* **2004**, *53*, 74–77.
7. Shi-Wen X, Racanelli M, Ali A, Simon A, Quesnel K, Stratton RJ, et al. Verteporfin inhibits the persistent fibrotic phenotype of lesional scleroderma dermal fibroblasts. *J. Cell Commun. Signal* **2021**, *15*, 71–80.
8. Papavassiliou KA, Sofianidi AA, Spiliopoulos FG, Gogou VA, Gargalionis AN, Papavassiliou AG. YAP/TAZ Signaling in the Pathobiology of Pulmonary Fibrosis. *Cells* **2024**, *13*, 1519.
9. Blom IE, Goldschmeding R, Leask A. Gene regulation of connective tissue growth factor: new targets for antifibrotic therapy? *Matrix Biol.* **2002**, *21*, 473–482.
10. Raghu G, Richeldi L, Fernández Pérez ER, De Salvo MC, Silva RS, Song JW, et al. ZEPHYRUS-1 Study Investigators. Pamrevlumab for Idiopathic Pulmonary Fibrosis: The ZEPHYRUS-1 Randomized Clinical Trial. *JAMA* **2024**, *332*, 380–389.
11. Pamrevlumab Combo Does Not Improve Survival in Advanced Pancreatic Cancer. Available online: <https://www.cancernetwork.com/view/pamrevlumab-combo-does-not-improve-survival-in-advanced-pancreatic-cancer> (accessed on 14 August 2025).
12. Leask A, Naik A, Stratton RJ. Back to the future: targeting the extracellular matrix to treat systemic sclerosis. *Nat. Rev. Rheumatol.* **2023**, *19*, 713–723.
13. Bork P. The modular architecture of a new family of growth regulators related to connective tissue growth factor. *FEBS Lett.* **1993**, *327*, 125–130.
14. Perbal A, Perbal B. The CCN family of proteins: a 25th anniversary picture. *J. Cell Commun. Signal* **2016**, *10*, 177–190.
15. Lau LF. Cell surface receptors for CCN proteins. *J. Cell Commun. Signal* **2016**, *10*, 121–127.
16. Mori T, Kawara S, Shinozaki M, Hayashi N, Kakinuma T, Igarashi A, et al. Role and interaction of connective tissue growth factor with transforming growth factor-beta in persistent fibrosis: A mouse fibrosis model. *J. Cell Physiol.* **1999**, *181*, 153–159.
17. Shi-wen X, Stanton LA, Kennedy L, Pala D, Chen Y, Howat SL, et al. CCN2 is necessary for adhesive responses to transforming growth factor-beta1 in embryonic fibroblasts. *J. Biol. Chem.* **2006**, *281*, 10715–10726.
18. Mori Y, Hinchcliff M, Wu M, Warner-Blankenship M, Lyons K, Varga J. Connective tissue growth factor/CCN2-null mouse embryonic fibroblasts retain intact transforming growth factor-beta responsiveness. *Exp. Cell Res.* **2008**, *314*, 1094–1104.
19. Liu S, Shi-wen X, Abraham DJ, Leask A. CCN2 is required for bleomycin-induced skin fibrosis in mice. *Arthritis Rheum.* **2011**, *63*, 239–246.
20. Wang Q, Usinger W, Nichols B, Gray J, Xu L, Seeley TW, et al. Cooperative interaction of CTGF and TGF-β in animal models of fibrotic disease. *Fibrogenes. Tissue Repair.* **2011**, *4*, 4.
21. Makino K, Makino T, Stawski L, Lipson KE, Leask A, Trojanowska M. Anti-connective tissue growth factor (CTGF/CCN2) monoclonal antibody attenuates skin fibrosis in mice models of systemic sclerosis. *Arthritis Res. Ther.* **2017**, *19*, 134.
22. Leask A. CCN2: a bona fide target for anti-fibrotic drug intervention. *J. Cell Commun. Signal.* **2011**, *5*, 131–133.
23. Leask A. Conjunction junction, what's the function? CCN proteins as targets in fibrosis and cancers. *Am. J. Physiol. Cell Physiol.* **2020**, *318*, C1046–C1054.
24. Ramazani Y, Knops N, Elmonem MA, Nguyen TQ, Arcolino FO, van den Heuvel L, et al. Connective tissue growth factor (CTGF) from basics to clinics. *Matrix Biol.* **2018**, *68–69*, 44–66.
25. Brenner MC, Krzyzanski W, Chou JZ, Signore PE, Fung CK, Guzman D, et al. FG-3019, a Human Monoclonal Antibody Recognizing Connective Tissue Growth Factor, is Subject to Target-Mediated Drug Disposition. *Pharm. Res.* **2016**, *33*, 1833–1849.
26. Neiens V, Hansbauer EM, Jaquin TJ, Peper-Gabriel JK, Mahavadi P, Snyder ME, et al. Preclinical concept studies showing advantage of an inhaled anti-CTGF/CCN2 protein for pulmonary fibrosis treatment. *Nat. Commun.* **2025**, *16*, 3251.

27. Overcoming Failures: Lessons From IPF Clinical Trials in the Past Year. Available online: <https://www.ajmc.com/view/overcoming-failures-lessons-from-ipf-clinical-trials-in-the-past-year> (accessed on 15 September 2025).
28. Trachalaki A, Lindahl AL, Petrarulo S, Margaritopoulos GA. “Regression to the truth”: lessons learned from negative IPF trials. *Breathe* **2025**, *21*, 240260.
29. Kurundkar AR, Kurundkar D, Rangarajan S, Locy ML, Zhou Y, Liu RM, et al. The matricellular protein CCN1 enhances TGF- β 1/SMAD3-dependent profibrotic signaling in fibroblasts and contributes to fibrogenic responses to lung injury. *FASEB J.* **2016**, *30*, 2135–2150.
30. Fischer AG, Elliott EM, Brittan KR, Garrett L, Sadri G, Aebbersold J, et al. Matricellular protein CCN1 promotes collagen alignment and scar integrity after myocardial infarction. *Matrix Biol.* **2024**, *133*, 14–32.
31. Quesnel K, Shi-Wen X, Hutchenreuther J, Xiao Y, Liu S, Peidl A, et al. CCN1 expression by fibroblasts is required for bleomycin-induced skin fibrosis. *Matrix Biol. Plus.* **2019**, *3*, 100009.
32. Königshoff M, Kramer M, Balsara N, Wilhelm J, Amarie OV, Jahn A, et al. WNT1-inducible signaling protein-1 mediates pulmonary fibrosis in mice and is upregulated in humans with idiopathic pulmonary fibrosis. *J. Clin. Investig.* **2009**, *119*, 772–787.
33. Riser BL, Barnes JL, Varani J. Balanced regulation of the CCN family of matricellular proteins: a novel approach to the prevention and treatment of fibrosis and cancer. *J. Cell Commun. Signal* **2015**, *9*, 327–339.
34. Peidl A, Perbal B, Leask A. Yin/Yang expression of CCN family members: Transforming growth factor beta 1, via ALK5/FAK/MEK, induces CCN1 and CCN2, yet suppresses CCN3, expression in human dermal fibroblasts. *PLoS ONE* **2019**, *14*, e0218178.