

1 **Pharmacological blockade of the WNT-beta-catenin signaling: a possible**
2 **first-in-kind DMOAD**

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18 **manuscript and are both corresponding authors**

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20 In the present issue of Osteoarthritis and Cartilage, Deshmukh and
21 colleagues identified a novel inhibitor of the Wnt-beta-catenin signaling
22 pathway, SM04690, and demonstrated that, in mice, a single intra-articular
23 injection was sufficient to protect from cartilage breakdown in a severe model of
24 instability-induced osteoarthritis ¹.

25 The pharmacological nature of the compound, its favorable
26 pharmacokinetic properties and the high tolerability in mice and humans ^{1,2}, at
27 least short term, make this finding extremely exciting, suggesting that the first
28 disease-modifying drug for osteoarthritis, the leading cause of disability
29 worldwide, is not anymore a mirage.

30 WNTs are secreted proteins that, by engaging with their receptors, can
31 activate several intracellular signaling pathways and elicit **diverse** types of
32 responses in different cells, including modulation of proliferation, differentiation
33 and acquisition of positional information. One such signaling pathway, the so-
34 called canonical WNT pathway, is mediated by the accumulation of the
35 intracellular messenger beta catenin and the consequent activation of a
36 transcriptional program mediated by TCF/LEF transcription factors (Fig. 1).
37 Activation of the canonical WNT pathway in chondrocytes activates several
38 processes **that contribute to osteoarthritis progression** including proliferation,
39 loss of differentiation and, in mature chondrocytes it mediates hypertrophic
40 differentiation ³ (Fig. 1).

41 Mechanical injury and inflammation are potent inducers of WNT
42 activation in cartilage ^{4,5}. Targeting canonical WNT signaling was justified by
43 abundant previous literature ³; for instance an allele of the WNT inhibitor Frzb
44 with diminished WNT-inhibitory capacity was found to be associated with
45 osteoarthritis in two different genetic association studies in humans ⁶. In mice,
46 loss of several molecules that suppress excessive activation of canonical WNT
47 signaling, including Frzb ⁷, Wnt16 ⁸, and Dot1l ⁹ resulted in increased WNT
48 activation and osteoarthritis.

49 The authors selected SM04690 by screening a library of compounds for
50 their capacity to suppress canonical WNT signaling in cell lines, and
51 subsequently in primary chondrocytes. Non-canonical WNT pathways, which
52 also affect cartilage biology¹⁰ were likely unaffected, at least based on regulation
53 of target genes.

54 As expected of a WNT antagonist, SM04690 supported chondrogenic
55 differentiation of mesenchymal stem cells *in vitro* with an EC50 at the low
56 nanomolar range. Less predictably, they also showed that SM04690 has also
57 anti-catabolic properties in that it inhibited cartilage extracellular matrix
58 breakdown and suppressed the expression of catabolic metalloproteinases.

59 *In vivo*, a single intraarticular injection of 0.3 micrograms of SM04690 one
60 week following severe destabilization prevented, to a certain extent, cartilage
61 breakdown in rats.

62 How could a single injection of a small compound result in such a long-
63 lasting effect in joints that are still destabilized? The authors suggest that
64 SM04690 has a pro-regenerative effect, but this is suggested only by the *in vitro*
65 data, whereas, *in vivo*, there is no direct evidence of regeneration (e.g. better
66 OARSI score after treatment than before). A different explanation may reside in
67 the remarkable pharmacokinetic properties of SM04690: one hundred eighty
68 days after a single injection the compound could still be detected well above
69 therapeutic levels in the cartilage, but at much lower level in bone, and was
70 hardly detected at any time point in the blood. These pharmacokinetic properties
71 are not typical for a small compound and suggest that SM04690 might
72 specifically bind and be retained in the cartilage. Accumulation and retention in
73 the cartilage not only explain the prolonged effect, but also the absence of
74 systemic adverse effects, which is also remarkable since WNT signaling is of
75 great importance in the homeostasis of most organs and systems.

76 Whilst our improved understanding of osteoarthritis pathogenesis has led
77 to the discovery of several therapeutic effective targets¹¹, it is the remarkable
78 specific and durable accumulation in cartilage that bring this technology
79 significantly closer to clinical translation by affording prolonged activity and low
80 toxicity.

81 The main limitation of this study is that we do not know the exact
82 mechanism of action of SM04690. Although it certainly suppresses excessive
83 activation of WNT signaling, how is this achieved? What molecule(s) does
84 SM04690 bind to? In fact, it is not clear if SM04690 suppresses WNT signaling
85 directly or, for instance, by affecting other pathways that in turn suppress WNT
86 signaling. The mechanism of action is of primary importance because several
87 attempts to inhibit WNT signaling at genetic level have failed to treat
88 osteoarthritis. For instance, Zhu et al.¹² inhibited canonical WNT signaling by
89 overexpressing the WNT inhibitor ICAT in chondrocytes but this resulted in
90 severe cartilage loss; Yasuhara et al. conditionally deleted beta catenin in
91 cartilage postnatally, which resulted in loss of the cartilage progenitor cells
92 expressing lubricin¹³. On the other hand, for instance, DKK-1 overexpression in
93 cartilage¹⁴ or bone¹⁵ improved the outcome of osteoarthritis in mice.

94 One additional limitation is that SM04690 was administered one week
95 after joint destabilization and therefore, although technically still in therapeutic
96 regime, one week after severe joint destabilization is a very early time point,
97 when osteoarthritis lesions are not fully established and the joint is in a state of

98 acute inflammation which is uncharacteristic of established osteoarthritis.
99 Therefore, this study does not closely represent what would be the typical
100 scenario in osteoarthritis patients, but rather reproduces a situation similar to
101 acute sports injuries, which ultimately predispose to osteoarthritis, or to very
102 early osteoarthritis. The inflammation in the early post-traumatic phases is
103 associated with activation of WNT signaling ⁴. It will be important to confirm
104 whether SM04690 is effective also in advanced osteoarthritis, when there is
105 established cartilage damage and marginal inflammation, or to be able to define
106 patients with early osteoarthritis who are likely to progress and therefore to
107 require treatment ¹⁶.

108 The timing and duration of the intervention will also be important. While
109 a prolonged and sustained activation of canonical WNT signaling is surely a
110 pathogenic event, a brief burst of WNT activation drives tissue repair in many
111 organs/systems including cartilage ³ (fig. 1) and it has been shown that a short-
112 controlled activation of this pathway also induces cartilage growth ³. This has
113 implications for the delivery of the compound. One hundred eighty days is a long
114 time for a mouse, but how does this translate to humans? What regime is right?
115 Inevitably, the answers will come from the several clinical studies started by this
116 group.

117 All the authors but one are affiliated to the biotech company SAMUMED,
118 who are pursuing clinical translation in humans. One completed phase I clinical
119 trial demonstrated safety over 24 weeks in 61 patients ² and, remarkably, also an
120 improvement of the joint space width (JSW). Replication and longer time points
121 will be needed in order to confirm the efficacy data for which this study is
122 underpowered and not purposely designed. Additional two phase II and one
123 phase III studies are ongoing.

124

125 **Figure legends**

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127 Fig. 1. Inflammatory and mechanical stimuli activate canonical WNT signaling in
128 cartilage. Controlled and transient activation ensures that homeostatic events
129 take place and supports stem cell renewal. Excessive activation leads to
130 osteoarthritis.

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132 **Authors' contribution**

133 F.D'A and F.C contributed equally to the design, the draft and the revision of the
134 manuscript.

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139 **Conflict of interest**

140 The authors declare no conflict of interest.

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