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

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

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

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

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

The authors selected SM04690 by screening a library of compounds for their capacity to suppress canonical WNT signaling in cell lines, and subsequently in primary chondrocytes. Non-canonical WNT pathways, which also affect cartilage biology [10] were likely unaffected, at least based on regulation of target genes.

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

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

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

Whilst our improved understanding of osteoarthritis pathogenesis has led to the discovery of several therapeutic effective targets [11], it is the remarkable specific and durable accumulation in cartilage that bring this technology significantly closer to clinical translation by affording prolonged activity and low toxicity.

The main limitation of this study is that we do not know the exact mechanism of action of SM04690. Although it certainly suppresses excessive activation of WNT signaling, how is this achieved? What molecule(s) does SM04690 bind to? In fact, it is not clear if SM04690 suppresses WNT signaling directly or, for instance, by affecting other pathways that in turn suppress WNT signaling. The mechanism of action is of primary importance because several attempts to inhibit WNT signaling at genetic level have failed to treat osteoarthritis. For instance, Zhu et al. [12] inhibited canonical WNT signaling by overexpressing the WNT inhibitor ICAT in chondrocytes but this resulted in severe cartilage loss; Yasuhara et al. conditionally deleted beta catenin in cartilage postnatally, which resulted in loss of the cartilage progenitor cells expressing lubricin [13]. On the other hand, for instance, DKK-1 overexpression in cartilage [14] or bone [15] improved the outcome of osteoarthritis in mice.

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

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

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

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

## Figure legends

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

## Authors' contribution

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


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## Conflict of interest

The authors declare no conflict of interest.

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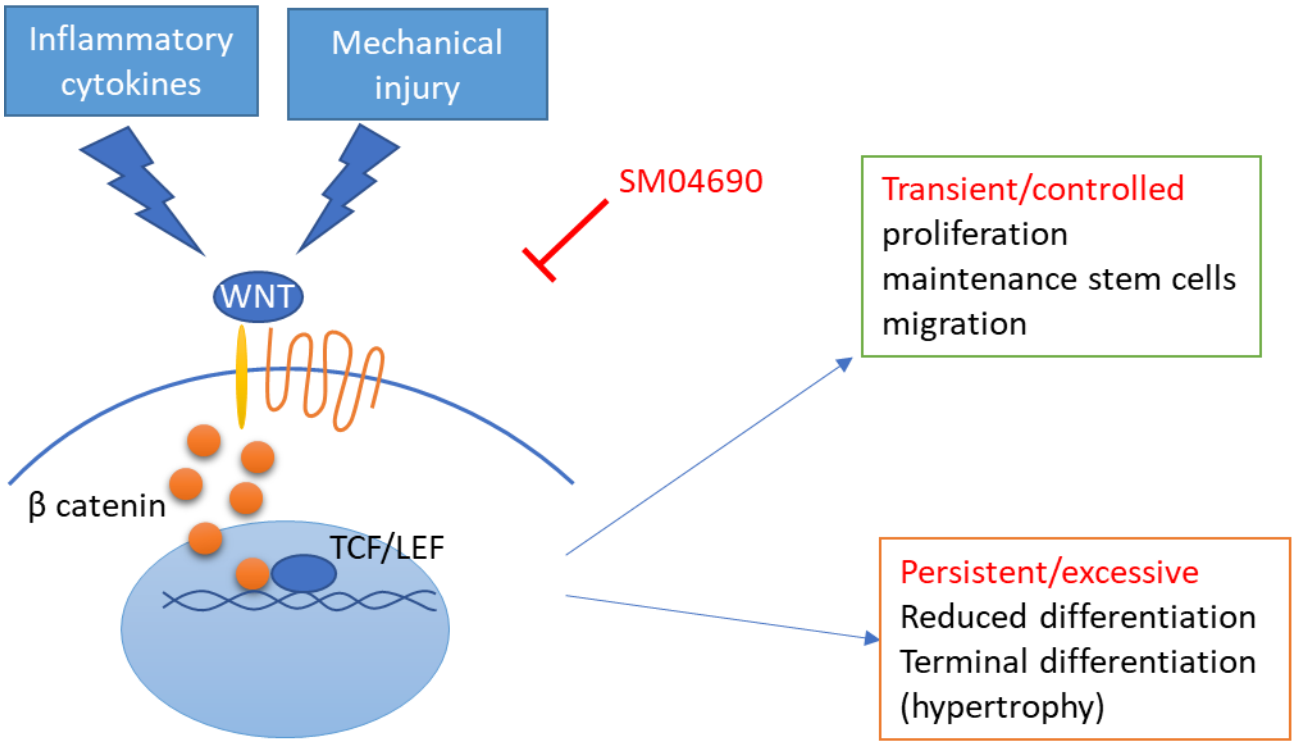
Inflammatory cytokines
Mechanical injury
SM04690
WNT
β catenin
TCF/LEF
Transient/controlled
proliferation
maintenance stem cells
migration
Persistent/excessive
Reduced differentiation
Terminal differentiation
(hypertrophy)