Our current siRNA-atelocollagen based technology requires IA injections too frequently to promote patient compliance. In the ML1 model of OA, blocking ROR2 in therapeutic regime using atelocollagen-conjugated siRNA resulted in reduced cartilage destruction and in rapid and sustained pain relief. Due to the limited expression pattern of ROR2 in adulthood, no systemic or local toxicity were expected, nor were any observed. With the current technology, ROR2 blockade requires intra-articular (IA) injections of siRNA conjugated to atelocollagen every 5 days. Preliminary efficacy data of potentially longer-acting ROR2 blockers are promising. The mechanism of action of ROR2 blockade was independent of modulation of canonical Wnt signaling. ROR2/WNT5A promoted nuclear localization of YAP, which required both Rho and G-proteins. YAP signaling downstream of ROR2 also required Rho, but not G-proteins. YAP and TEAD inhibition was required, but not sufficient, for the chondrogenic effect of blocking ROR2. Therefore, additional, yet unknown mechanisms must be involved downstream of ROR2.

Conclusion: ROR2 blockade has potential as a disease-modifying treatment for OA, resulting in cartilage protection and rapid and sustained pain relief in a murine model. This will be crucial for clinical success of any treatment for OA and for OA, resulting in cartilage protection and rapid and sustained pain relief in a murine model. This will be crucial for clinical success of any treatment for OA.

## Acknowledgements
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## Disclosure of Interests
Anne-Sophie Thorup: None declared, Danielle Strachan: None declared, Sara Caixar: None declared, Blandine Poulet: None declared, Bethan Thomas: None declared, Suzanne Eldridge: None declared, Giovanna Naless: None declared, James Whiterford: None declared, Costantino Pitzalis: None declared, Thomas Agner: None declared, Roger Corder: None declared, Jessica Bertrand: None declared, Francesco Dell’Accio Consultant of: Samumed and UCB

## References

## Results
We demonstrate the dynamic changes in O-GlcNAcylation during osteoclast differentiation.

## Methods
We examined the levels of O-GlcNac during in vitro osteoclastogenesis by western blotting. The levels of O-GlcNac in tissue from RA patients and experimental arthritis were detected by immunofluorescence. Pharmacological inhibitor and genetic knockout were used to modulate O-GlcNAcylation during osteoclastogenesis. RNA sequencing was performed to study O-GlcNAcylation-mediated pathways.

## Discussion of Interests
Chih-Wei Chen: None declared, Yi-Nan Li: None declared, THONG THINH-MINH: None declared, ZHU Honglin: None declared, Alexandre-Emil Matei: None declared, XIAO Ding: None declared, DUONG Tran Manh: None declared, XIAOHAN Xu: None declared, Christoph Liebel: None declared, Francesco Dell'Accio Consultant of: Samumed and UCB.

## References

## Results
We demonstrate the dynamic changes in O-GlcNAcylation during osteoclastogenesis. The elevated O-GlcNAcylation was found in the early differentiation stages, whereas its downregulation was detected in the maturation process. TNFα elaborates the dynamic changes in O-GlcNAcylation, which further intensifies osteoclast differentiation. Targeting OGT by selective inhibitor and genetic knockout restrain O-GlcNAcylation and hinder the expression of the early differentiation marker Nfatc1. Inhibition of OGA, which forces high levels of O-GlcNAcylation throughout the differentiation, reduces the formation of multinucleated mature osteoclasts. Consistent with our in vitro data, suppressing OGT and OGA both ameliorate bone loss in experimental arthritis. We detected a reduced number of TRAP-expressing precursors and mature osteoclasts in the mice subjected to OGT inhibition. While inhibiting OGA only lowers the number of TRAP−/F4/80− mature osteoclasts without affecting the number of TRAP−/F4/80+ precursors. Transcriptome profiling reveals that O-GlcNAcylation regulates several biological processes. Increased O-GlcNAcylation promotes cytokine signaling and oxidative phosphorylation. The downregulation of O-GlcNAcylation is essential for cytoskeleton organization and cell fusion.

## Conclusion
We demonstrate that the dynamic changes of O-GlcNAcylation are essential for osteoclast differentiation. These findings reveal the therapeutic potential of targeting O-GlcNAcylation in pathologic bone resorption.

## Disclosure of Interests
Chih-Wei Chen: None declared, Yi-Nan Li: None declared, THONG THINH-MINH: None declared, ZHU Honglin: None declared, Alexandre-Emil Matei: None declared, XIAO Ding: None declared, DUONG Tran Manh: None declared, XIAOHAN Xu: None declared, Christoph Liebel: None declared, Francesco Dell’Accio Consultant of: Samumed and UCB.
declared, Ruifang Liang: None declared, Min-Chuan Huang: None declared, Neng-Yu Lin: None declared, Andreas Rammig Speakers bureau: Boehringer Ingelheim, Roche, Janssen, Consultant of: Boehringer Ingelheim, Novartis, GlaxoSmithKline, Pfizer. Grant/research support from: Pfizer, Novartis, Georg Schett, Speakers bureau: AbbVie, BMS, Celgene, Janssen, Eli Lilly, Novartis, Roche and UCB, Jörg H.W. Distler Shareholder of: 4D Science, Speakers bureau: Boehringer Ingelheim, Paid instructor for: Boehringer Ingelheim, Consultant of: Actelion, Active Biotech, Anamar, ARFX, Bayer Pharma, Boehringer Ingelheim, Celgene, Galapagos, GSK, Inventiva, JB Therapeutics, Medac, Pfizer, RPR and UCB, Grant/research support from: Anamar, Active Biotech, Array, Biopharma, aTyr, BMS, Bayer Pharma, Boehringer Ingelheim, Celgene, Galapagos, GSK, Inventiva, Novartis, Sanofi-Aventis, RedX, UCB, Employee of: FibroCure.

Drs.

Table 1. Relative Risk of Gout by Body Mass Index, Stratified by Mean Genetic Score

<table>
<thead>
<tr>
<th>BMI</th>
<th>Below Mean</th>
<th>Above Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-Years</td>
<td>20000</td>
<td>40000</td>
</tr>
<tr>
<td>Person-Years</td>
<td>20000</td>
<td>40000</td>
</tr>
<tr>
<td>Age-Adjusted</td>
<td>1.0 (ref)</td>
<td>1.80 (1.23, 2.57)</td>
</tr>
<tr>
<td>RR</td>
<td>1.88 (1.35, 2.65)</td>
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<tr>
<td>MV Adjusted*</td>
<td>1.0 (ref)</td>
<td>1.80 (1.23, 2.57)</td>
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<tr>
<td>MV Adjusted*</td>
<td>1.0 (ref)</td>
<td>2.84 (1.92, 3.92)</td>
</tr>
<tr>
<td>RR</td>
<td>2.65 (1.88, 3.45)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age (continuous), menopause, use of hormone therapy (never, past or current), history of hypertension, and systolic and diastolic blood pressure, alcohol, total energy intake and intake of meat, seafood and dairy foods (all continuous).

References:

[1] Safiri et al., PMID 32375051
[2] Xia et al., PMID 31624843
[3] Tin et al., PMID 31578528

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