# 17° MEETING FOP ITALIA
# 4 aprile 2025
# Seebay Hotel Portonovo (Ancona)

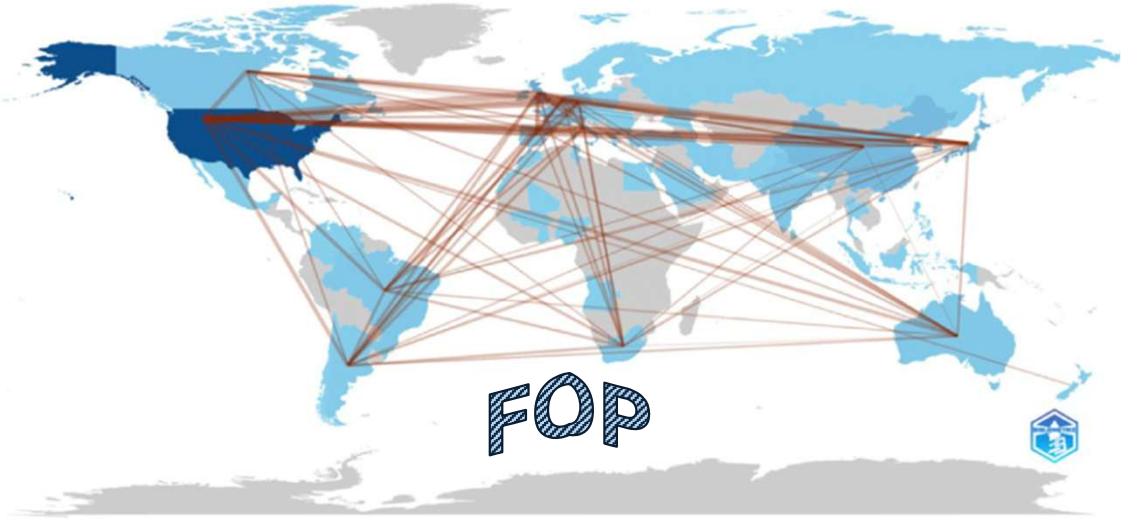
## Panoramica sulle recenti ricerche


Renata Bocciardi & Serena Cappato

DINOGMI Università degli Studi di Genova
UOC Genetica Medica IRCCS Giannina Gaslini

# Update of the research on FOP

# Aggiornamenti sulla ricerca




EFORT Open Reviews (2024) 9 589–599
https://doi.org/10.1530/EOR-23-0207

# Fibrodysplasia Ossificans Progressiva

**Gene therapy**

~~**Anti Alk2 antibodies (DS-6016a)**~~

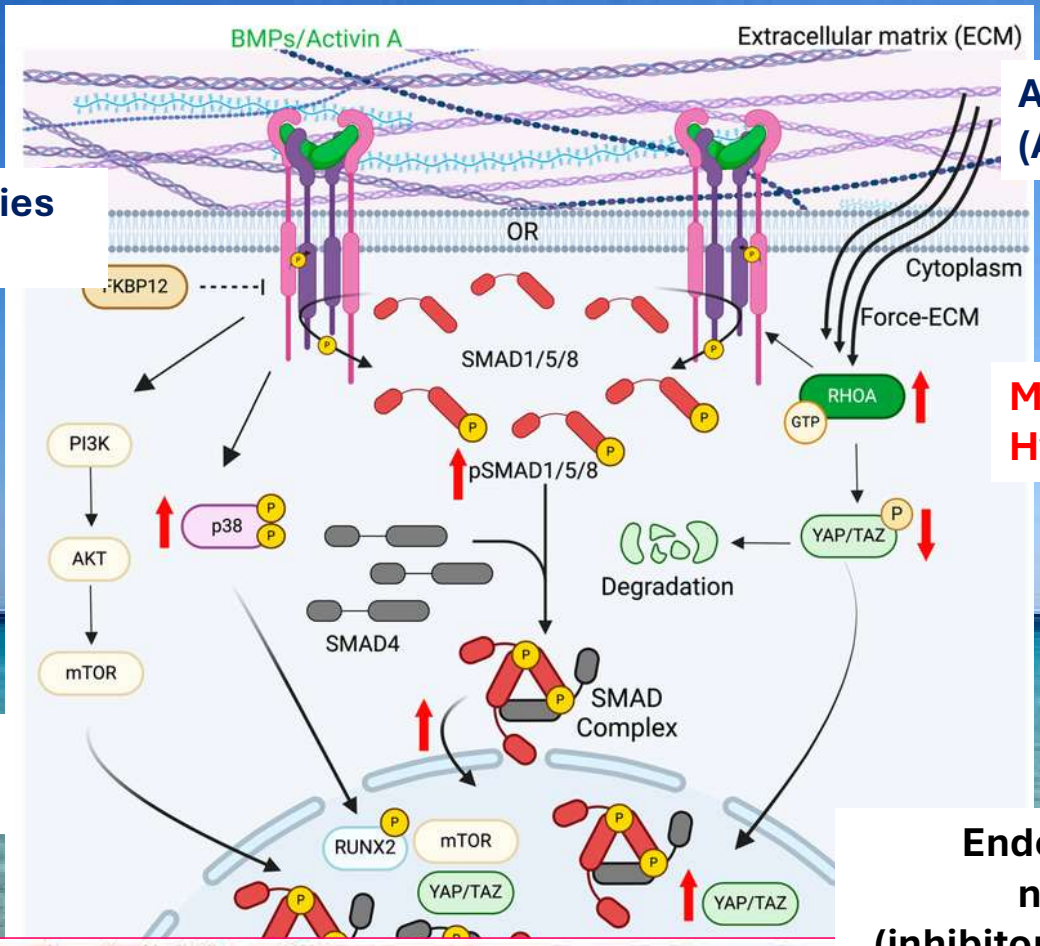
**Anti-ActA antibodies (Garetosmab)**

**Kinase inhibitors**

1. **IPN60130/Fidrisertib**
2. **INC000928/Zilurgisertib**
3. **Saracatinib (AZD0530)**
4. ~~**BX9250**~~
5. **KER-47**

**Inflammation**

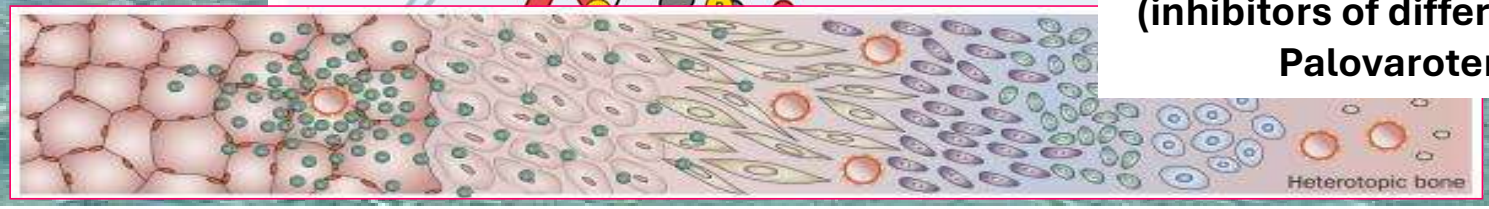
**Canakinumab (anti IL1B)**




**Anti-MMP antibodies (Andecaliximab)**

**Microenvironment, Hypoxia, autophagy**

**Endochondral bone neoformation (inhibitors of differentiation - Palovarotene)**



## Gene therapy

"Sviluppo di una terapia selettiva con siRNA per la FOP"
"Development of a SNP selective siRNA therapeutic for the Treatment of FOP"
**David Cooper** (UMass Chan Medical School, Worcester)

"Sviluppo di una terapia combinata con siRNA per la FOP"
"Development of a Combinatorial siRNA Therapy for the Treatment of FOP"
**Katherine Gross** (UMass Chan Medical School, Worcester)

## Anti-ActA antibodies

"Aggiornamenti da Regeneron" – "Regeneron updates"
**Regeneron Pharmaceuticals, Inc.**

## Kinase inhibitors

"Saracatinib per la prevenzione dell'HO dopo l'intervento chirurgico e il ruolo dell'attivina B nella FOP"
"Saracatinib for the prevention of HO after surgery and the role of activin B in FOP"
**Paul Yu** (Harvard Medical School, Boston)

"Aggiornamenti trial Stopfop e attività presso il FOP Expertise Center/Rare Bone Disease Center Amsterdam UMC"
"Stopfop trial updates and activities at the FOP Expertise Center/Rare Bone Disease Center Amsterdam UMC"
**Marelise Eekhoff** (VU University Medical Center, Amsterdam)

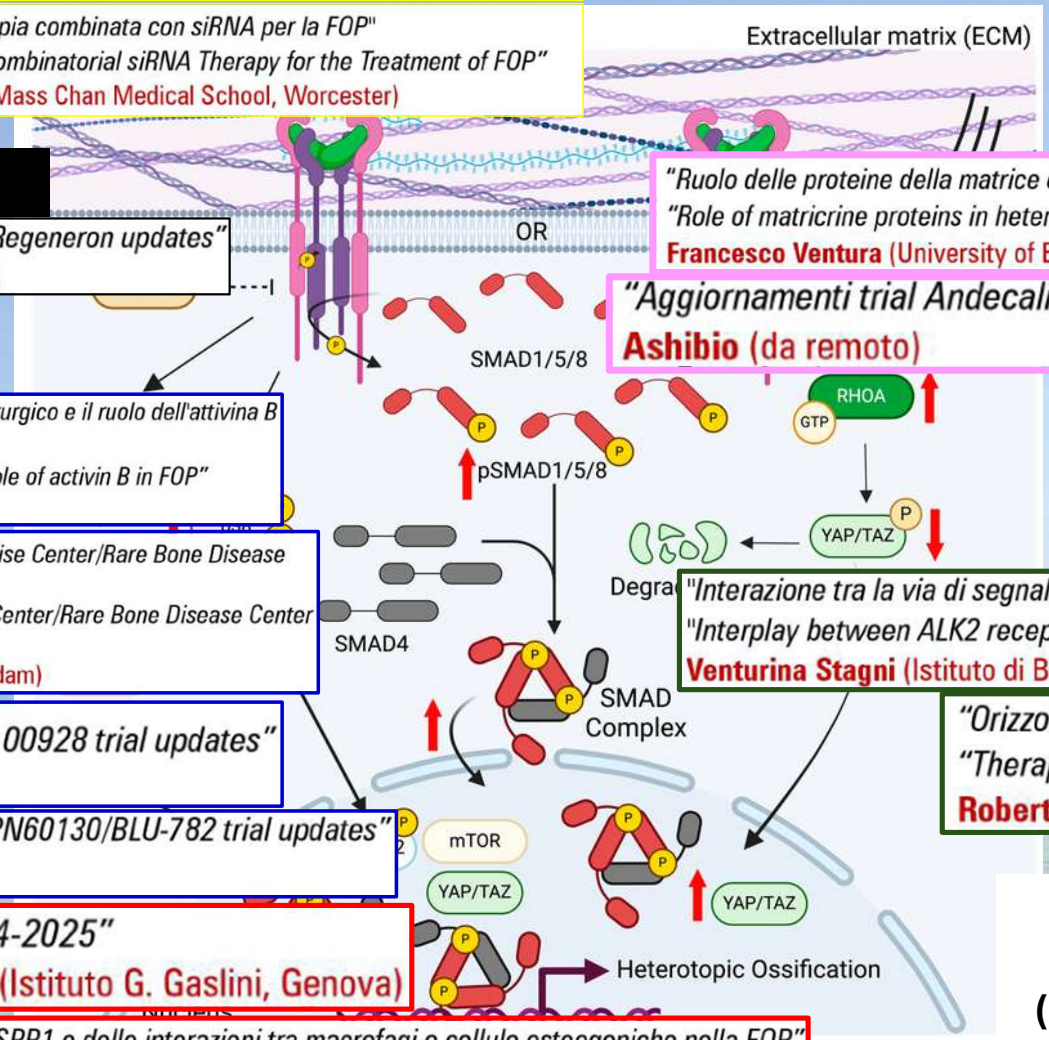
"Aggiornamenti trial INCB 00928" – "INCB 00928 trial updates"
**Incyte Biosciences Italy**

"Aggiornamenti trial IPN60130/BLU-782" – "IPN60130/BLU-782 trial updates"
**Ipsen Spa**

## Inflammation

"FOP news 2024-2025"
**Riccardo Papa** (Istituto G. Gaslini, Genova)

"Analisi sul ruolo di SPP1 e delle interazioni tra macrofagi e cellule osteogeniche nella FOP"
"Exploring the Role of SPP1 and Macrophage-Osteogenic Cell Crosstalk in FOP"
**Silvia Brunelli** (Università degli Studi di Milano Bicocca, Milano)




## ECM & Proteases

"Ruolo delle proteine della matrice extracellulare nella formazione dell'osso eterotopico"
"Role of matricrine proteins in heterotopic bone formation"
**Francesco Ventura** (University of Barcelona)

"Aggiornamenti trial Andecaliximab" – "Andecaliximab trial updates"
**Ashibio** (da remoto)

## Microenvironment, Hypoxia, autophagy

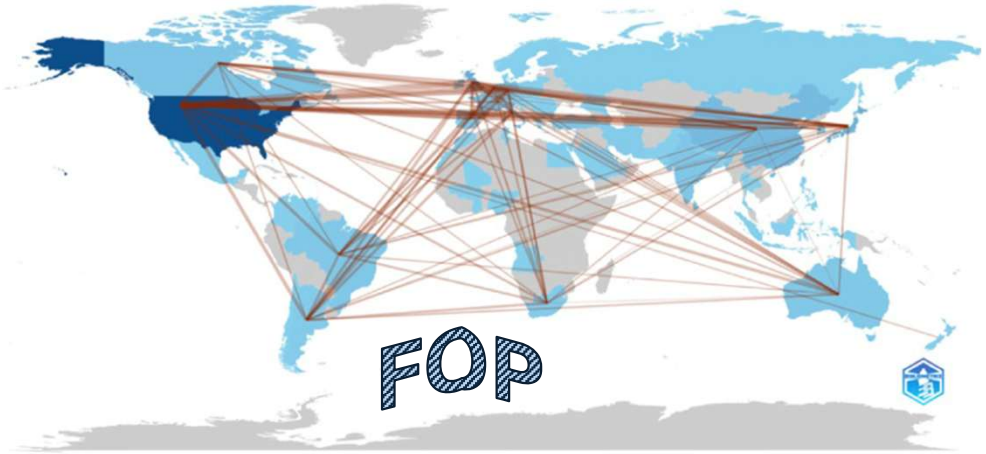
"Interazione tra la via di segnalazione autofagica e del recettore ALK2 nella FOP"
"Interplay between ALK2 receptor signaling and autophagy in FOP"
**Venturina Stagni** (Istituto di Biologia e Patologia Molecolari - IBPM di Roma)

"Orizzonti terapeutici nella FOP"
"Therapeutic Horizons in FOP"
**Robert Pignolo** (Majo Clinic, Rochester) da remoto

**Endochondral bone neoformation (inhibitors of differentiation - Palovarotene)**

# Update of the research on FOP

## Aggiornamenti sulla ricerca




*News & Views*

OPEN ACCESS · CHECK FOR UPDATES

EMBO Molecular Medicine

## Targeting to BMP9 to restrain flare-up of fibrodysplasia ossificans progressiva

Qiwen Li & Quan Yuan ✉

*Article*

SOURCE DATA · TRANSPARENT PROCESS · OPEN ACCESS · CHECK FOR UPDATES

EMBO Molecular Medicine

## BMP-9 mediates fibroproliferation in fibrodysplasia ossificans progressiva through TGF-β signaling

Chengzhu Zhao [1,2]✉, Yoshiko Inada[2], Souta Motoike[2], Daisuke Kamiya [2,3], Kyosuke Hino[2,4] & Makoto Ikeya [2,3]✉

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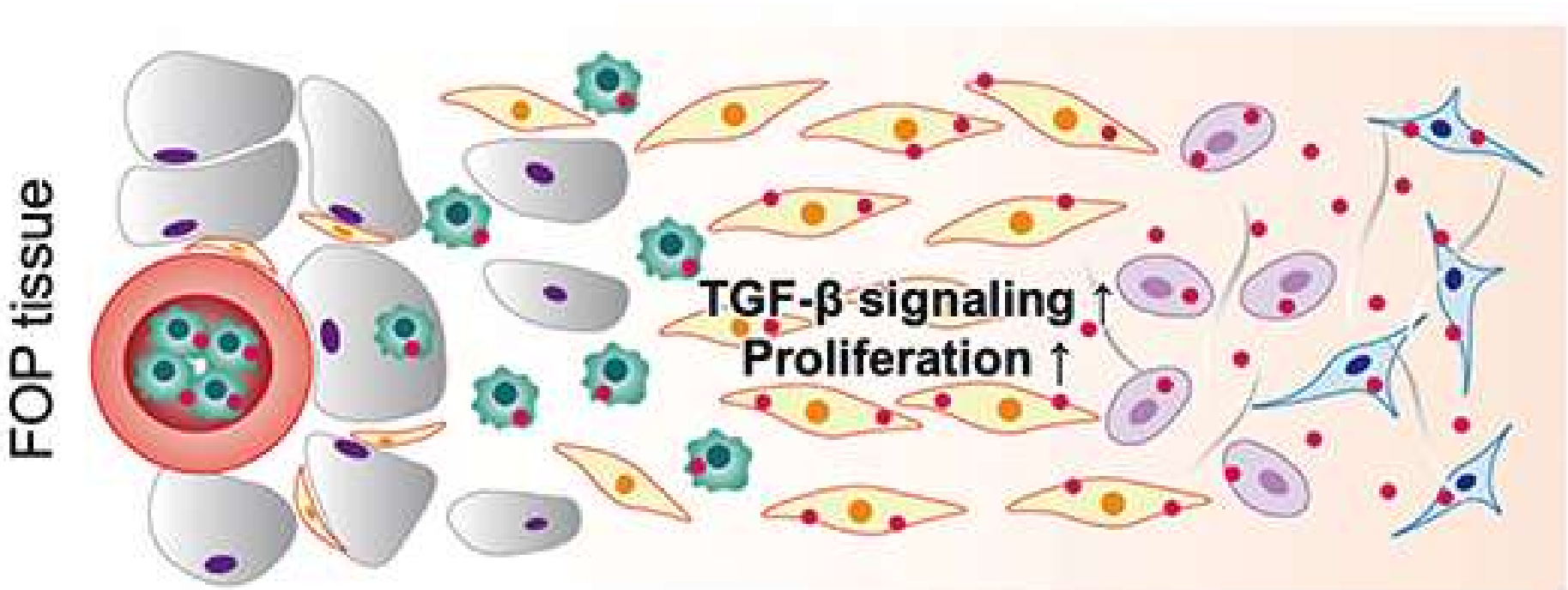
# BMP9 as a target for FOP therapy?




**Degenerazione del muscolo**

**Risposta infiammatoria**

**Formazione di tessuto fibroproliferativo (MSCs/FAP)**

https://doi.org/10.1038/s44321-024-00174-3

# Have we ever heard about BMP9?

Junia Toguchida
Kyoto University
Kyoto, Japan

PNAS

## Neofunction of ACVR1 in fibrodysplasia ossificans progressiva

Kyosuke Hino[a,b], Makoto Ikeya[a,1], Kazuhiko Horigome[a,b], Yoshihisa Matsumoto[a,c,d], Hayao Ebise[e], Megumi Nishio[a], Kazuya Sekiguchi[a,c,f], Mitsuaki Shibata[a], Sanae Nagata[a], Shuichi Matsuda[f], and Junya Toguchida[a,c,f,1]

[a]Department of Cell Growth and Differentiation, Center for iPS Cell Research and Application, Kyoto University, Kyoto, 606-8507, Japan; [b]iPS Cell-Based Drug Discovery Group, Innovative Drug Discovery Laboratories, Sumitomo Dainippon Pharma Co., Ltd., Osaka, 554-0022, Japan; [c]Department of Tissue Regeneration, Institute for Frontier Medical Sciences, Kyoto University, Kyoto, 606-8507, Japan; [d]Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Nagoya City University, Nagoya, 467-8601, Japan; [e]Omics Group, Genomic Science Laboratories, Sumitomo Dainippon Pharma Co., Ltd., Osaka, 554-0022, Japan; and [f]Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, Kyoto, 606-8507, Japan

GENETIC DISORDERS

Science Translational Medicine

## *ACVR1*$^{R206H}$ receptor mutation causes fibrodysplasia ossificans progressiva by imparting responsiveness to activin A

Sarah J. Hatsell,[1]* Vincent Idone,[1]* Dana M. Alessi Wolken,[1†] Lily Huang,[1†] Hyon J. Kim,[1†] Lili Wang,[1] Xialing Wen,[1] Kalyan C. Nannuru,[1] Johanna Jimenez,[1] Liqin Xie,[1] Nanditha Das,[1] Genevieve Makhoul,[1] Rostislav Chernomorsky,[1] David D'Ambrosio,[1] Richard A. Corpina,[1] Christopher J. Schoenherr,[1] Kieran Feeley,[1‡] Paul B. Yu,[2] George D. Yancopoulos,[1] Andrew J. Murphy,[1] Aris N. Economides[1,3§]

Aris Economides
Regeneron
Terrytown, New York (USA)

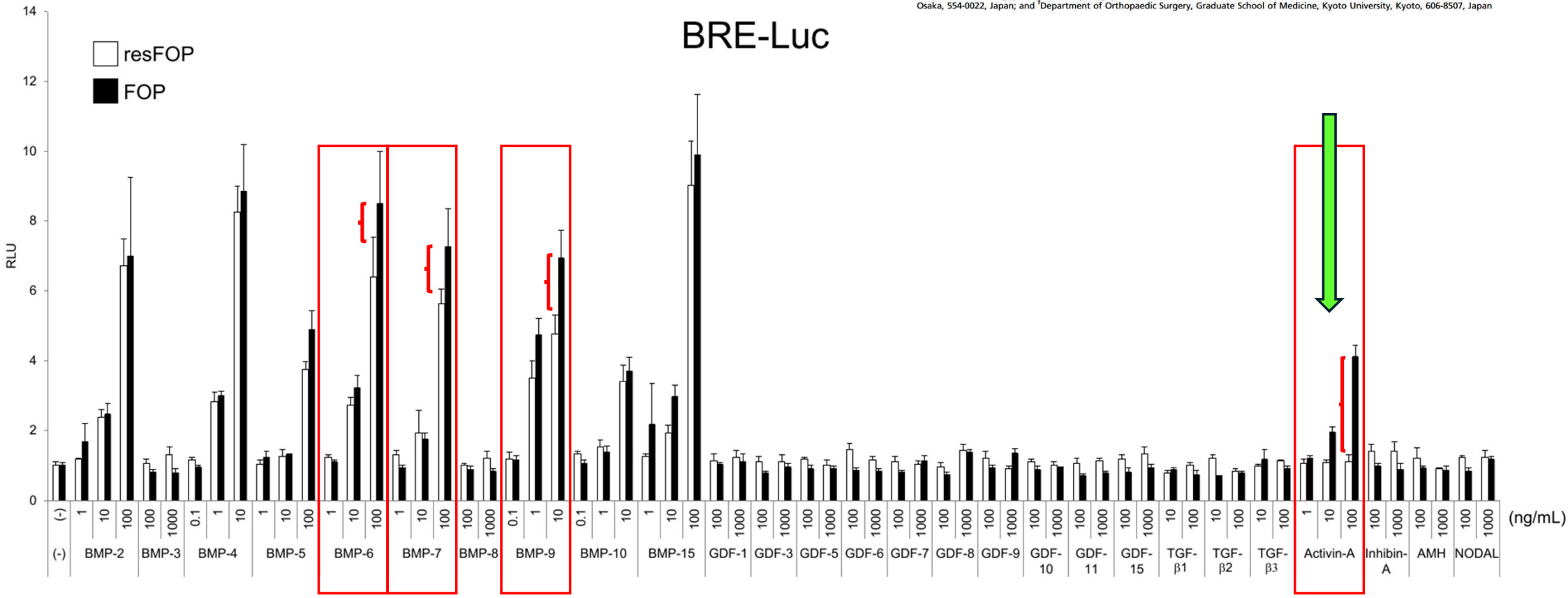
Hatsell et al., Sci Transl Med. 2015 Sep 2;7(303):303ra137; Hino et al., Proc Natl Acad Sci U S A. 2015 Dec 15;112(50):15438-43.

PNAS

# Neofunction of ACVR1 in fibrodysplasia ossificans progressiva

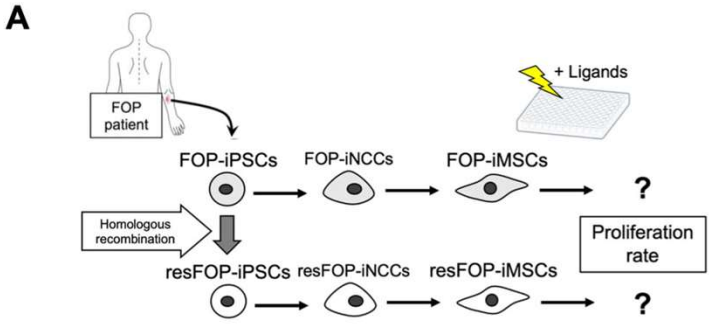
Kyosuke Hino[a,b], Makoto Ikeya[a,1], Kazuhiko Horigome[a,b], Yoshihisa Matsumoto[a,c,d], Hayao Ebise[e], Megumi Nishio[a], Kazuya Sekiguchi[a,c,f], Mitsuaki Shibata[a], Sanae Nagata[a], Shuichi Matsuda[f], and Junya Toguchida[a,c,f,1]

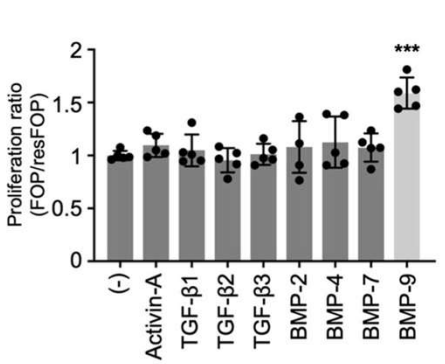
[a]Department of Cell Growth and Differentiation, Center for iPS Cell Research and Application, Kyoto University, Kyoto, 606-8507, Japan; [b]iPS Cell-Based Drug Discovery Group, Innovative Drug Discovery Laboratories, Sumitomo Dainippon Pharma Co., Ltd., Osaka, 554-0022, Japan; [c]Department of Tissue Regeneration, Institute for Frontier Medical Sciences, Kyoto University, Kyoto, 606-8507, Japan; [d]Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Nagoya City University, Nagoya, 467-8601, Japan; [e]Omics Group, Genomic Science Laboratories, Sumitomo Dainippon Pharma Co., Ltd., Osaka, 554-0022, Japan; and [f]Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, Kyoto, 606-8507, Japan



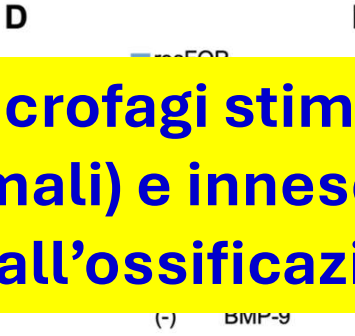

Hino K et al. Neofunction of ACVR1 in fibrodysplasia ossificans progressiva. Proc Natl Acad Sci U S A. 2015 Dec 15;112(50):15438-43. doi: 10.1073/pnas.1510540112. PMID: 26621707

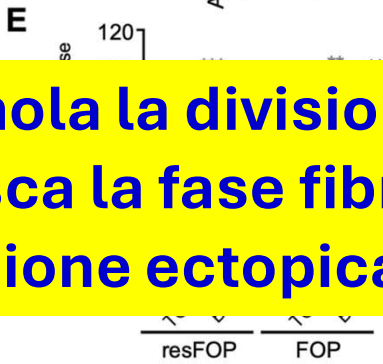
**Abnormal proliferation of FOP-iMSCs and flare-ups triggered by BMP-9 in FOP-ACVR1 transgenic mice**



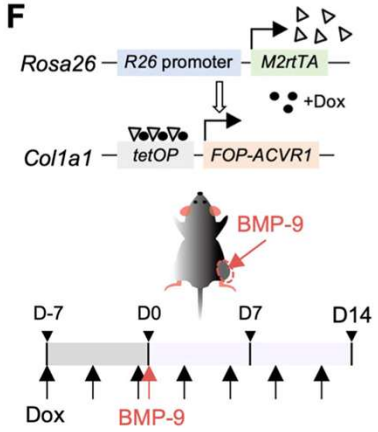



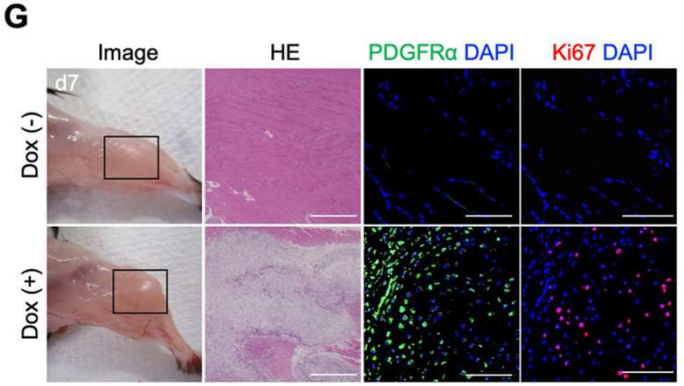


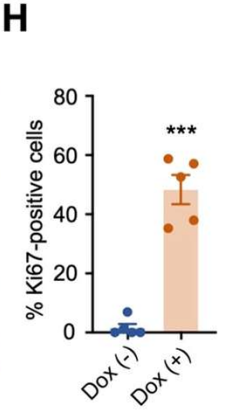


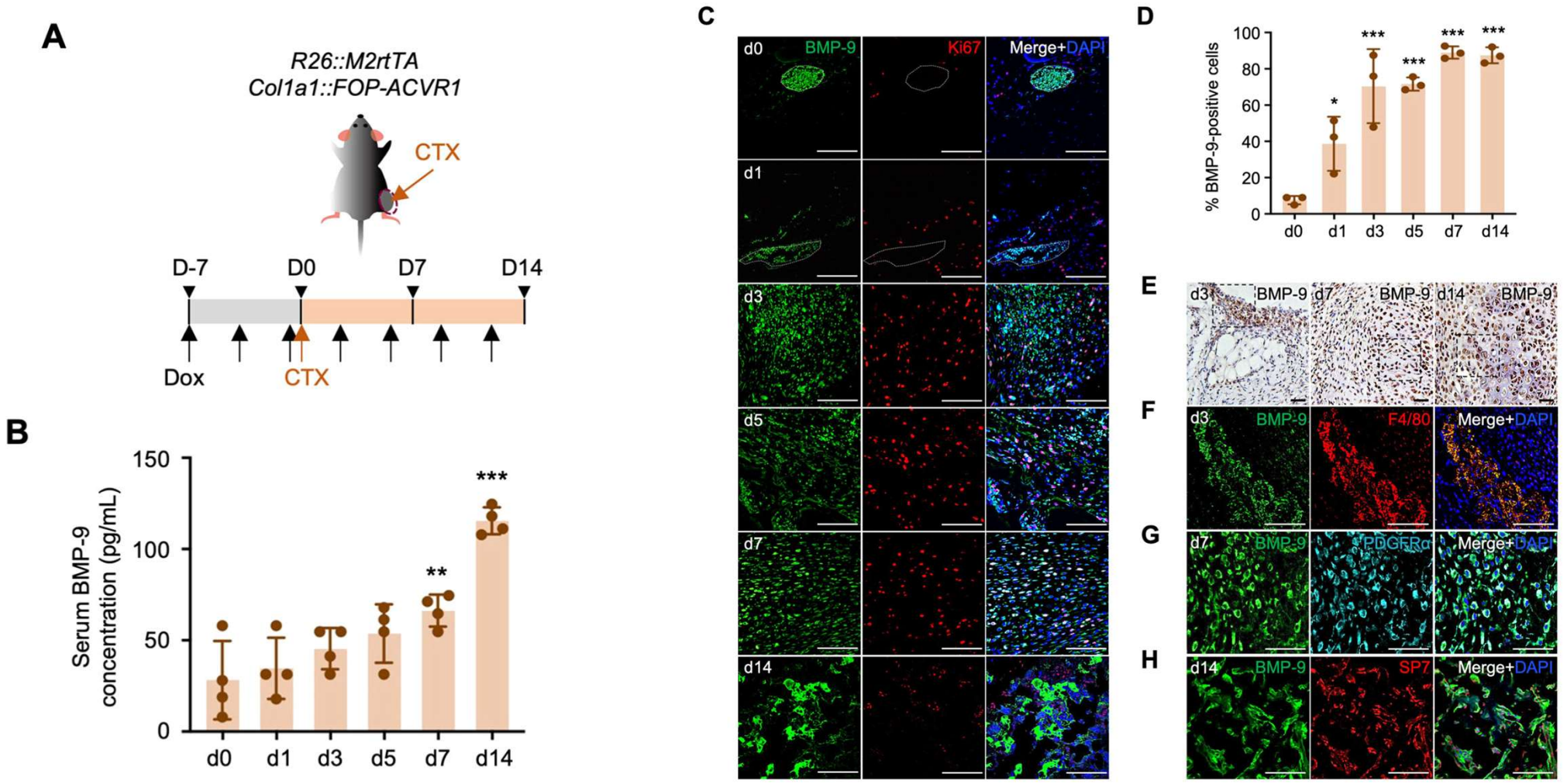

**La BMP9 prodotta dai macrofagi stimola la divisione delle cellule progenitrici (mesenchimali) e innesca la fase fibroproliferativa che porta all'ossificazione ectopica**



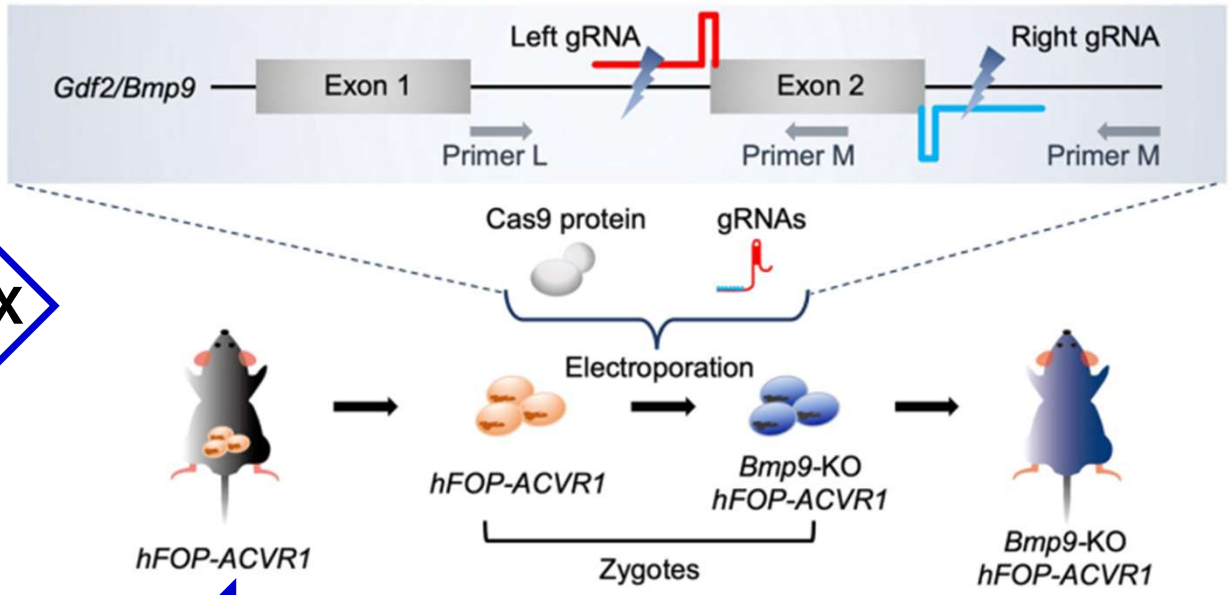



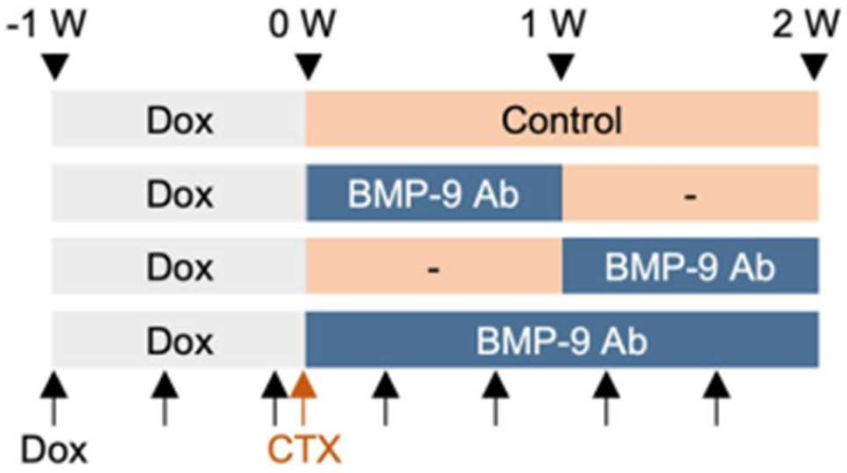
# Increased BMP-9 expression in CTX-injected tissue of FOP mice



# Does BMP9 is a druggable target for FOP?

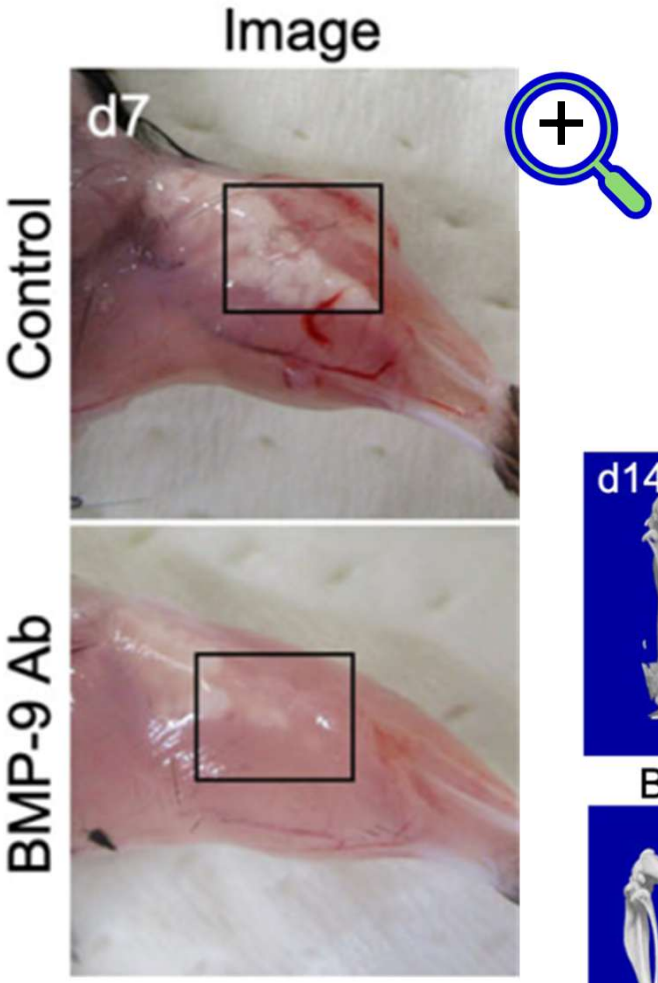
**Bmp9-KO-hFOP-ACVR1 transgenic mice exhibit attenuated HO after CTX injection.**

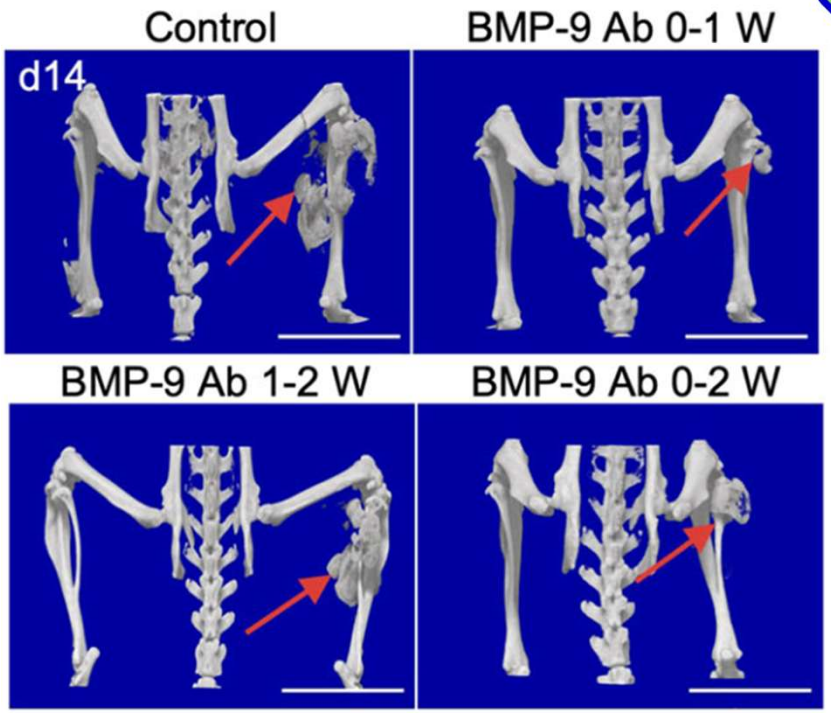


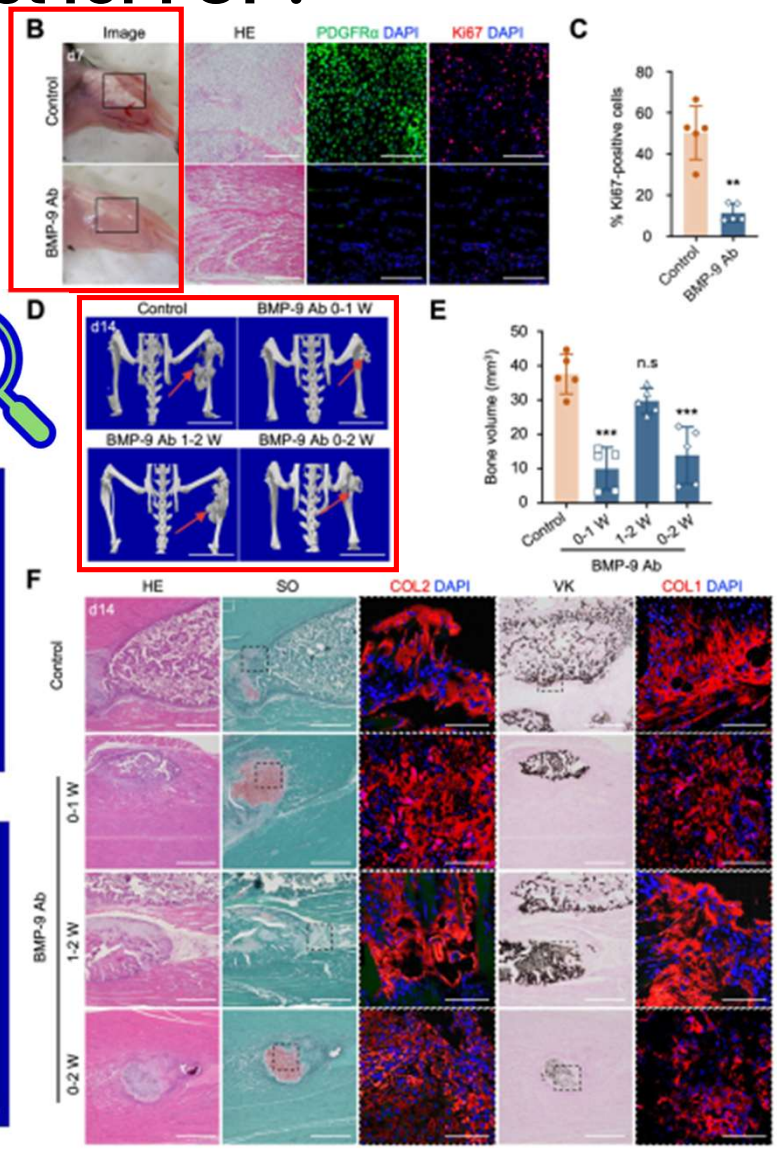




**Systemic BMP-9 neutralizing antibody administration mitigates earlBmp9-KO-hFOP-ACVR1y FOP lesions and HO progression in CTX-induced FOP mice.**

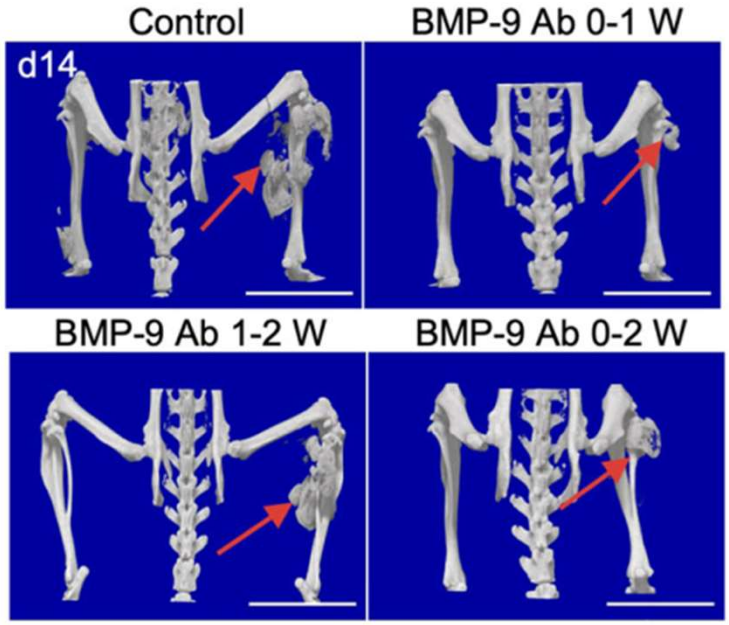
# Does BMP9 is a druggable target for FOP?

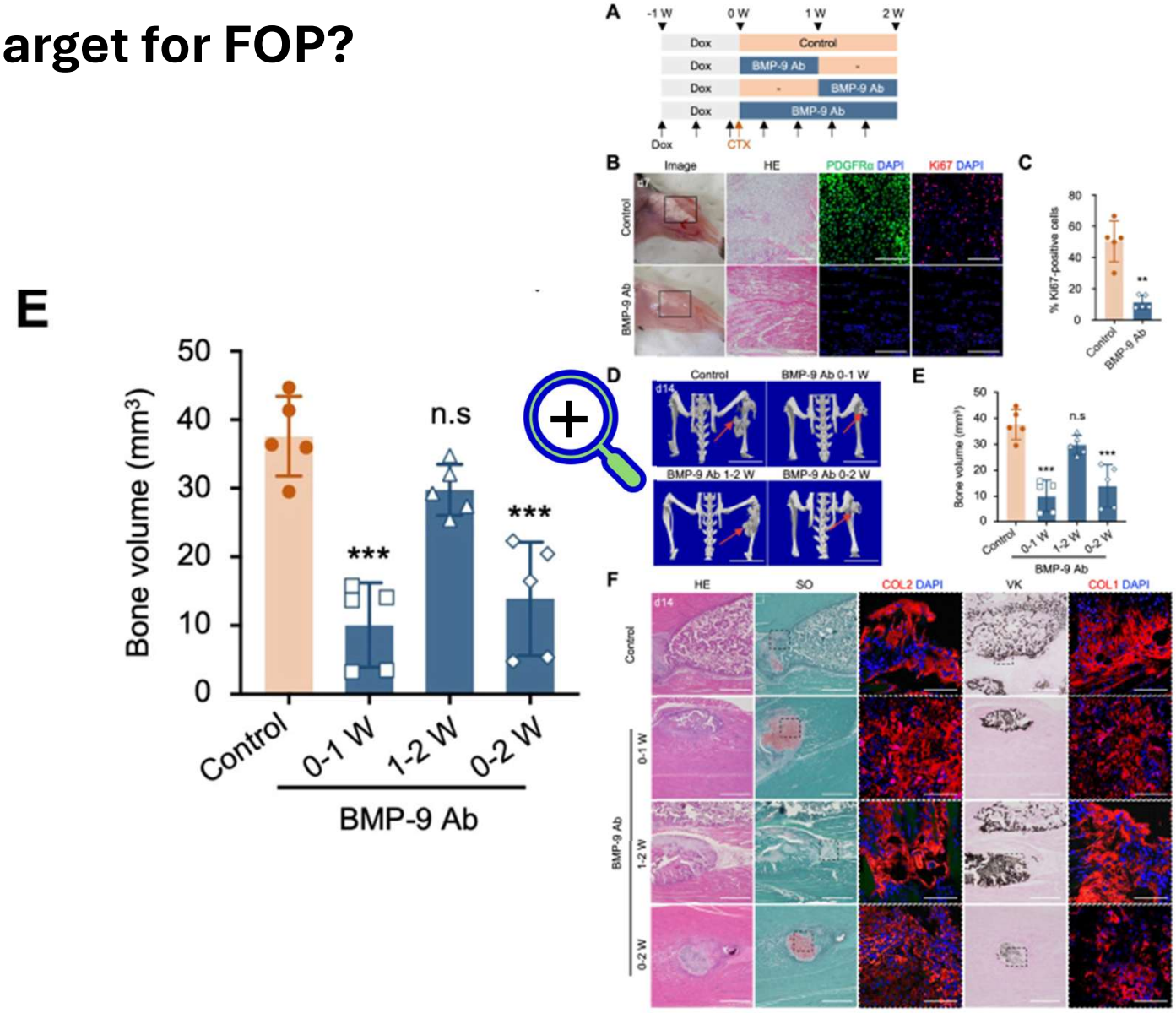


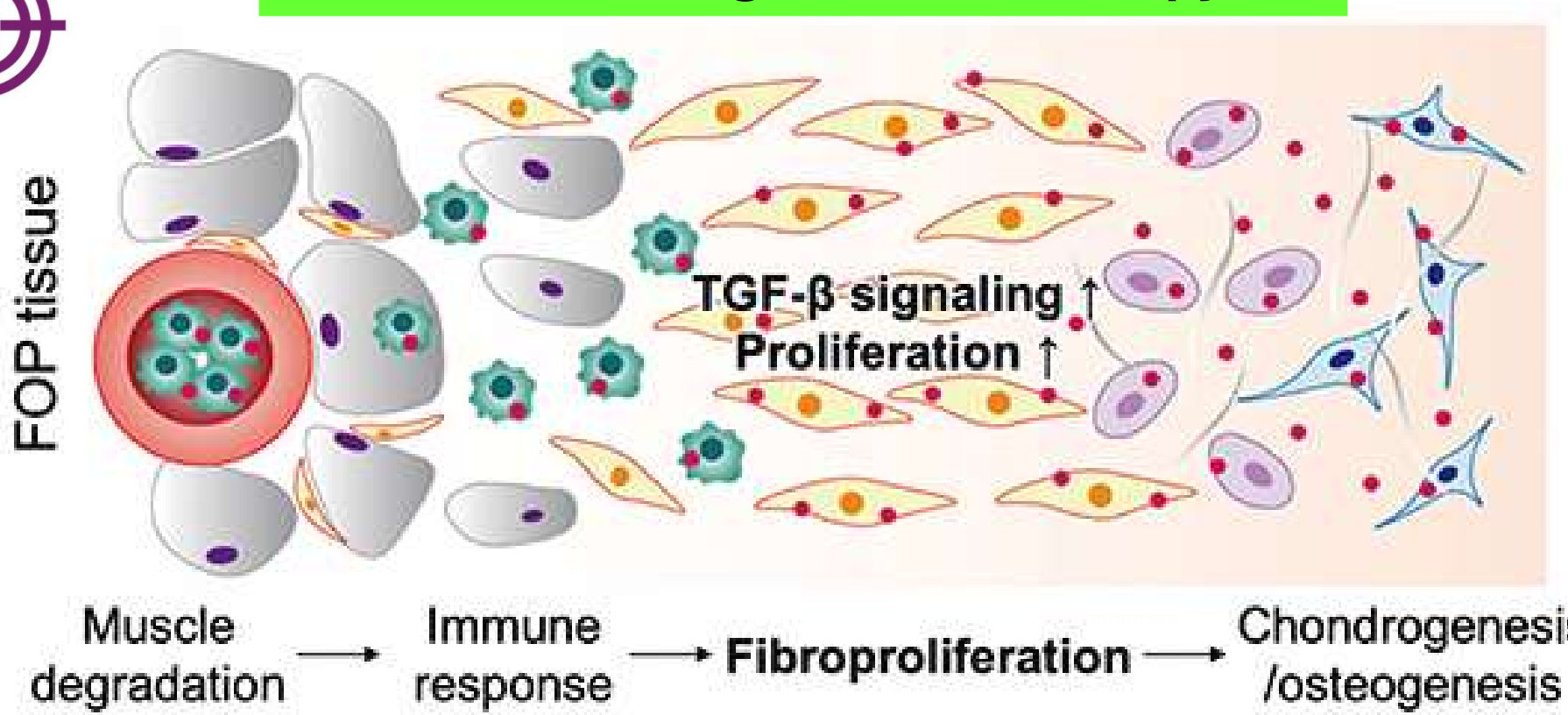



# Does BMP9 is a druggable target for FOP?



# BMP9 as a target for FOP therapy




**Interventions targeting BMP-9 or TGF-β signaling elements may represent a therapeutic option for early-stage FOP, offering valuable insights into advancing FOP treatment strategies**

BMP-9

# Update of the research on FOP

# Aggiornamenti sulla ricerca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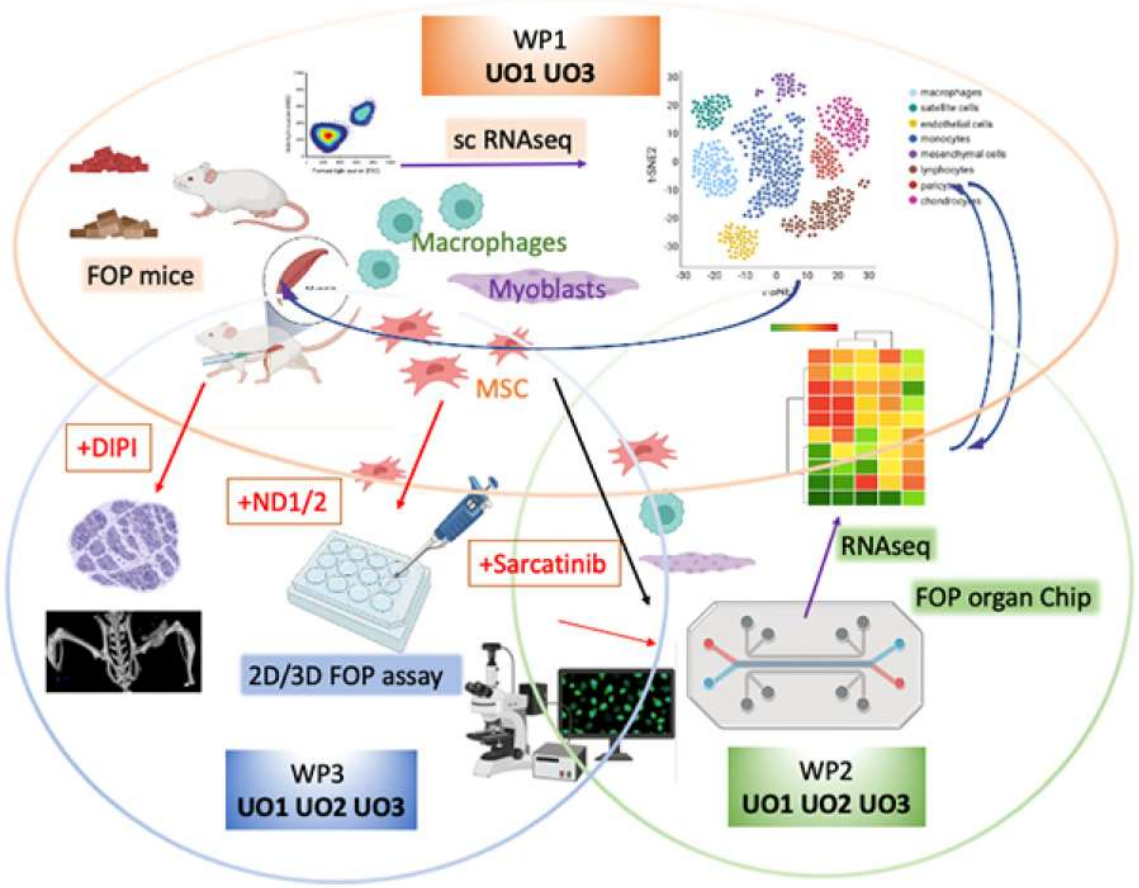
Ministero dell'Università e della Ricerca

PRIN
PROGETTI DI RICERCA DI RILEVANTE INTERESSE NAZIONALE – 2022
Prot. 2022TR9N4R

# Environmental control oF Ectopic oSTeOgenesis in Fibrodysplasia Ossificans Progressiva: from mouse to chip and back (EFESTO)




**UO1**
**Silvia Brunelli, PI**
**Responsabile Progetto**
**Riccardo Gamberale**
**Mauro Bergamaschi**

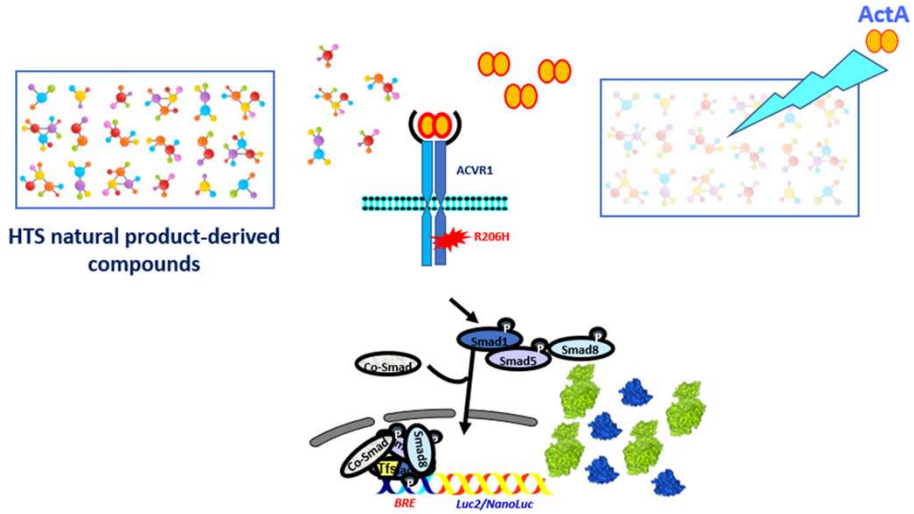
**UO2**
**Paolo Netti**
**Francesco Urciuolo**

**UO3**
**Renata Bocciardi**
**Serena Cappato**
**Michela Bellardita**

# Screening of Natural product-derived compounds

- **Primary Screening of 300 natural derived compounds**
- **196 commercially available analogues**

√

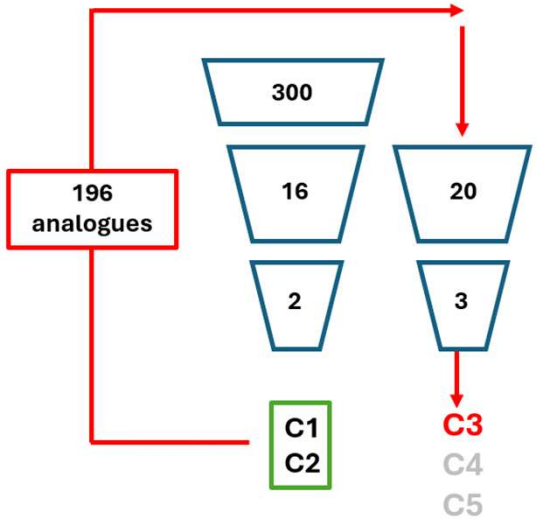



**Confirmation:**

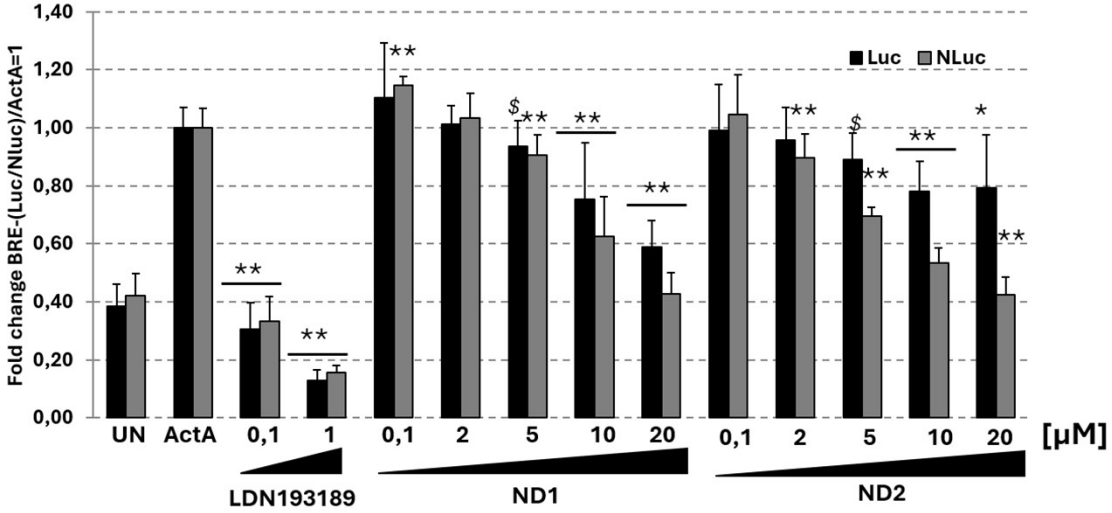
- **Dose-response curves**
- **Toxicity evaluation (MTT assay)**
- ***Id1* & *Id3* genes expression**

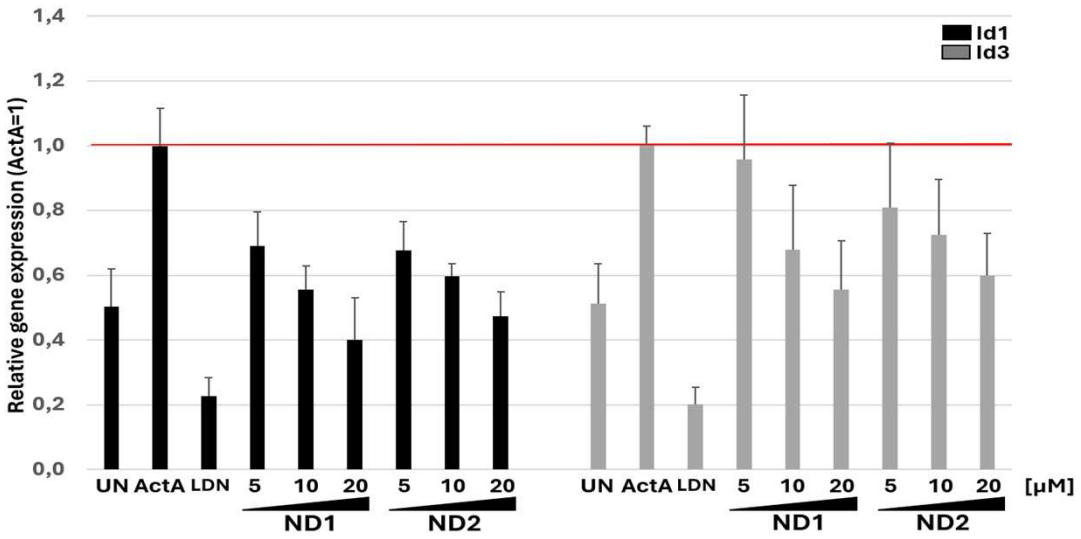
√

- **ActA vs BMP2**
- **Effect on canonical and non canonical P-Smads**
- ***In vitro* differentiation (micromass cultures)**
- **Ex-vivo & In-vivo analysis (FOP mouse)**



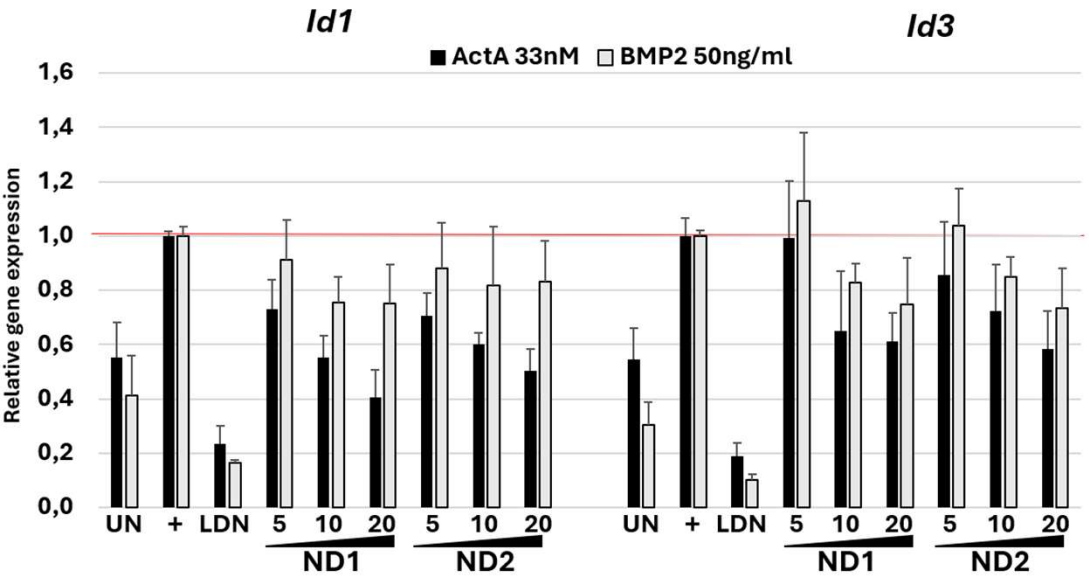
# ND1 and ND2: effect on the reporter gene (dose-response)



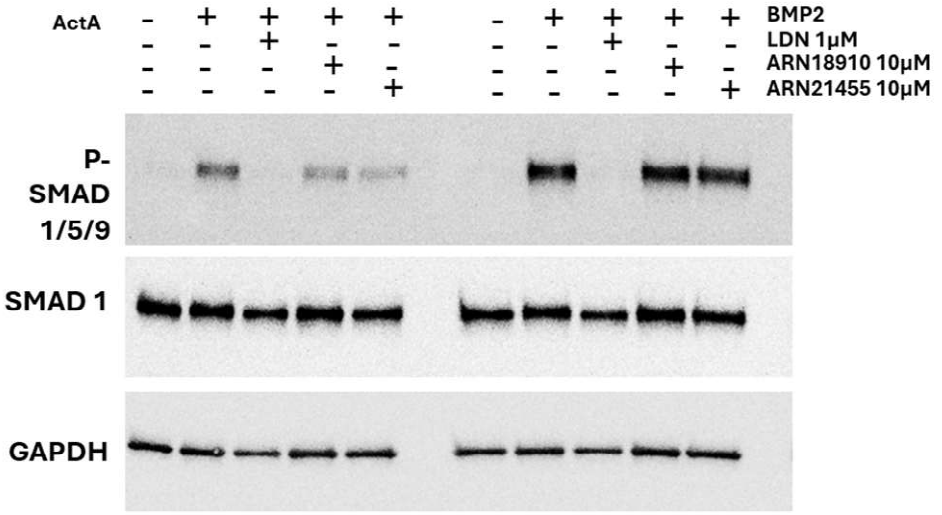



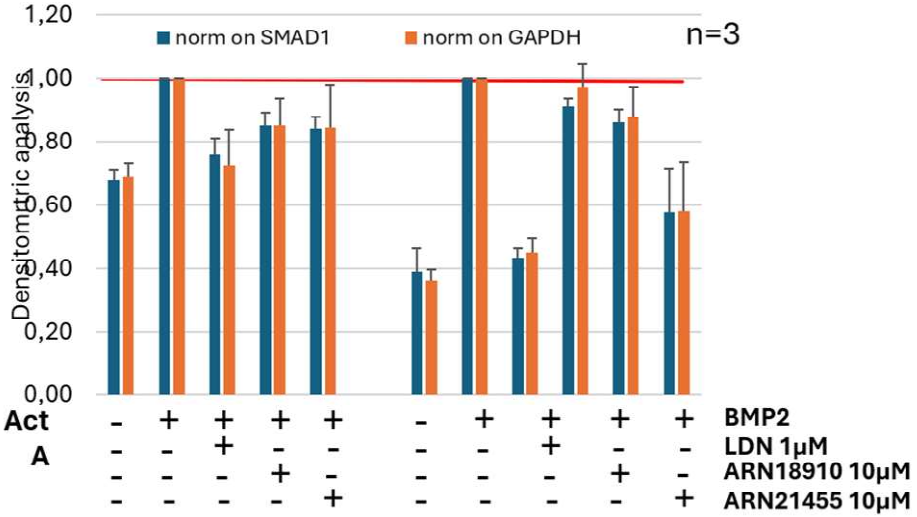

n=2-5 ( $, $p < 0.05$ *, $p < 0.01$;** p<0.001 relative to ActA) Mann-Whitney non parametric test

# ActA vs BMP2



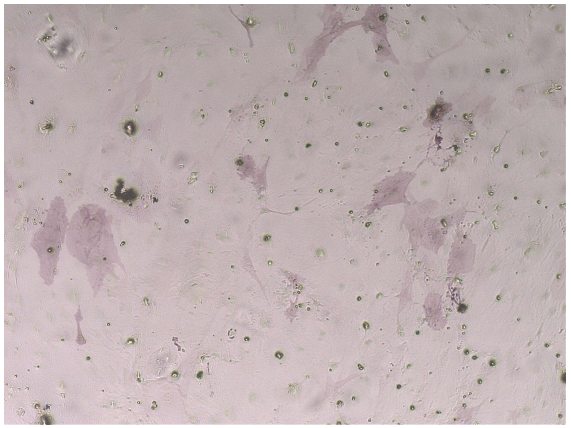

# ND1 & ND2 & effect on SMAD1/5/9 signaling



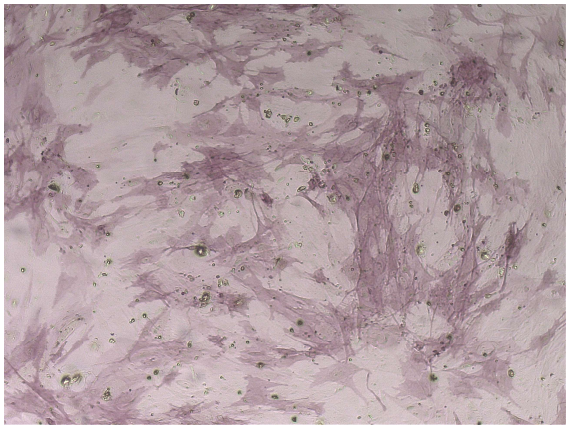



# Effect of selected natural compound on osteogenic FAP_R206H differentiation

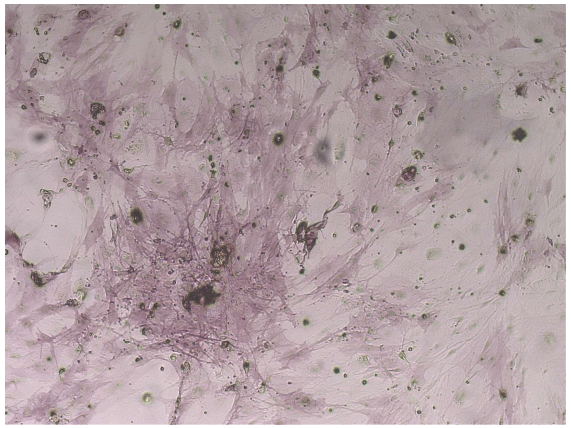
NT



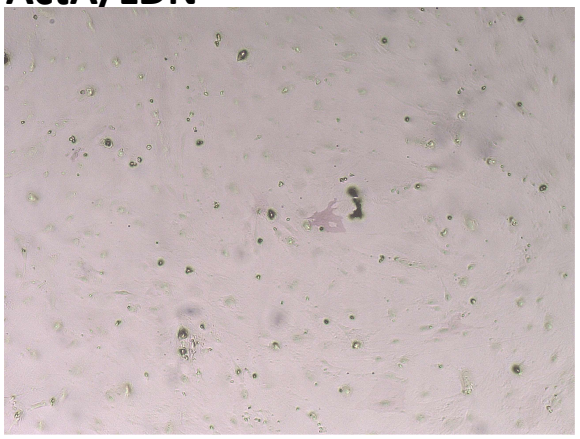
ActA



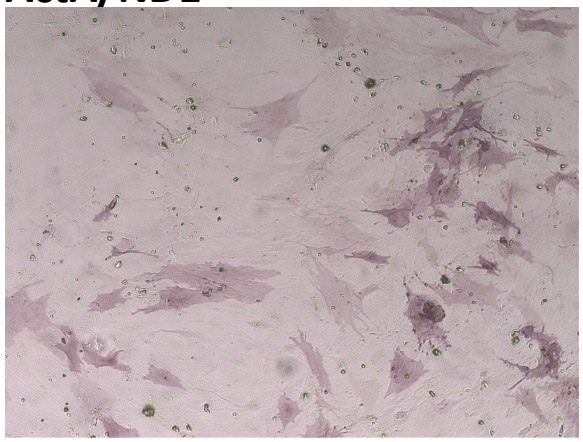
BMP-2



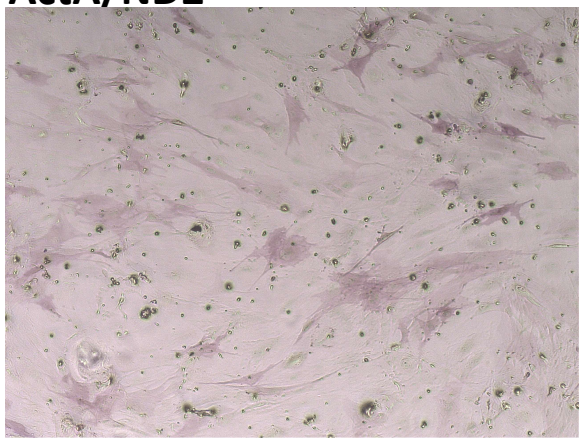
ActA/LDN



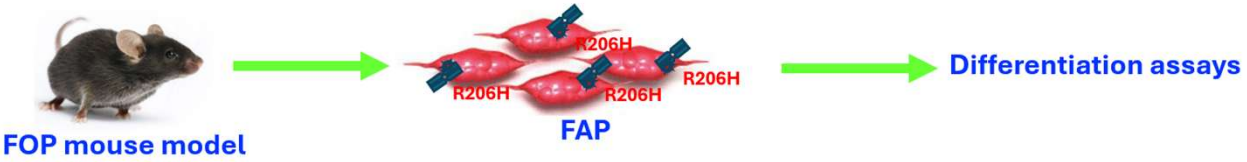
ActA/ND1



ActA/ND2



ALP staining



# Screening of Natural product-derived compounds: identification of 2 (+1) active compounds

- Primary Screening of 300 natural derived compounds
- 196 commercially available analogues

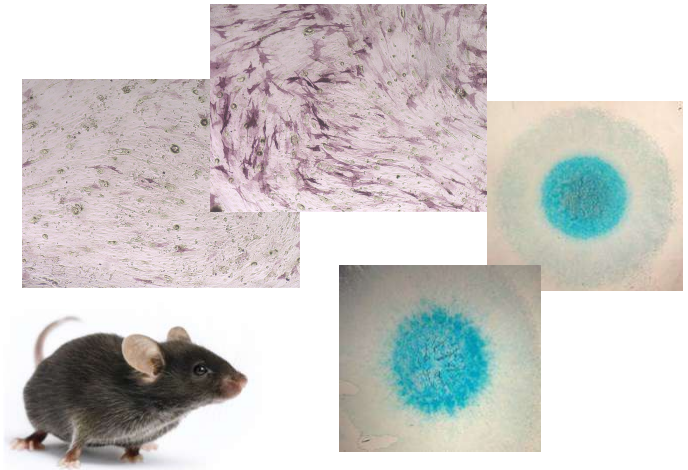
√

**Confirmation:**

- Dose-response curves
- Toxicity evaluation (MTT assay)
- *Id1* & *Id3* genes expression

√

- ActA vs BMP2
- Effect on canonical and non canonical P-Smads
- *In vitro* differentiation (micromass cultures)
- *Ex-vivo* & *In-vivo* analysis (FOP mouse)



# *Collaborations & funding & Acknowledgement*

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**Ricerca corrente**

**PRIN**
**PROGETTI DI RICERCA DI RILEVANTE INTERESSE NAZIONALE – 2022**
**Prot. 2022TR9N4R**

**Fondi per la Ricerca di Ateneo**
**Università di Genova**

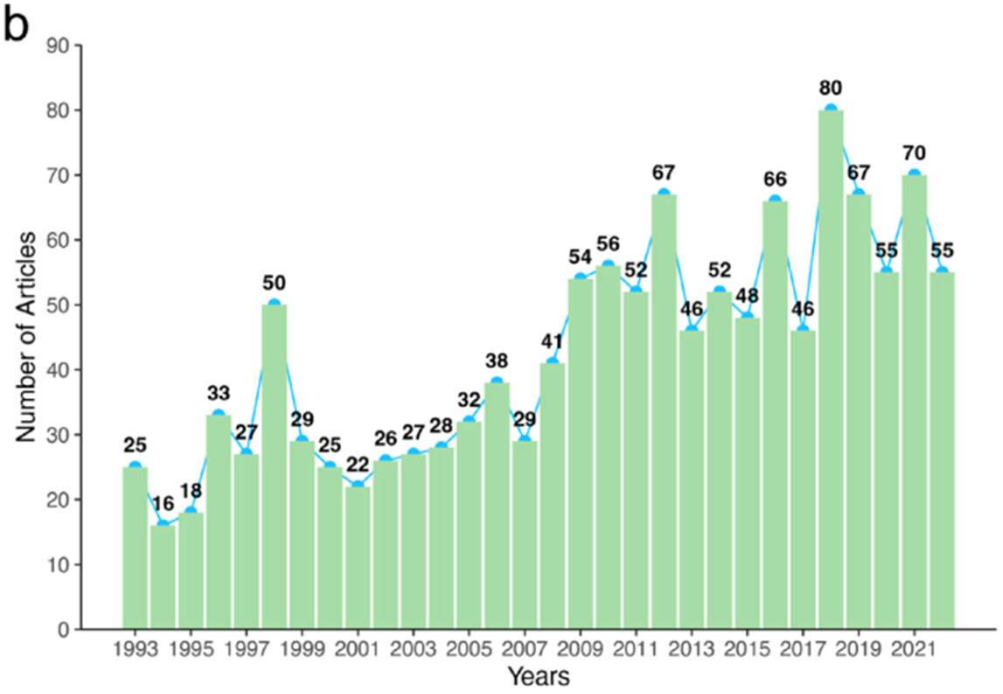
EFORT open reviews

*EFORT Open Reviews* (2024) **9** 589–599
https://doi.org/10.1530/EOR-23-0207

GENERAL ORTHOPAEDICS

# Research trends and hotspots of myositis ossificans: a bibliometric analysis from 1993 to 2022

Bowen Lai*, Heng Jiang*, Yuan Gao and Xuhui Zhou




Myositis ossificans (MO) is characterized by benign heterotopic ossificans in soft tissues like muscles, which can be classified into nonhereditary MO and fibrodysplasia ossificans progressiva (FOP).

The annual number of publications and related research areas in the MO field increased gradually in the past 20 years. The USA contributed the most percentage (42.58%) of articles. The University of Pennsylvania (UPenn) and the Journal Bone published the most articles among all institutions and journals. Kaplan FS and Shore EM from UPenn were the top two scholars who made the largest contributions to this field.

Keyword analysis showed that research hotspots changed from traumatic MO and clinical management of MO to the genetic etiology, pathogenesis, and treatment of FOP.

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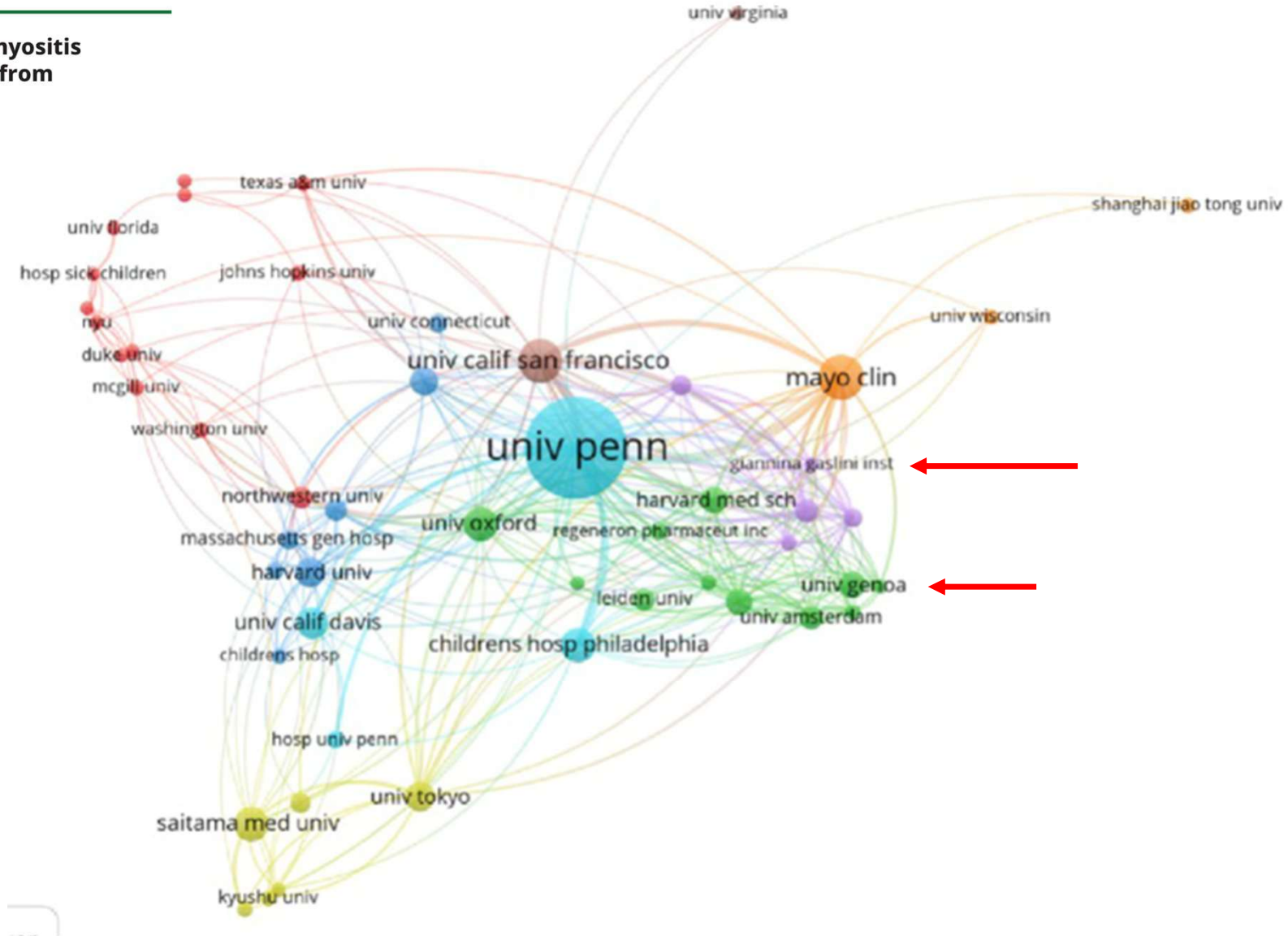
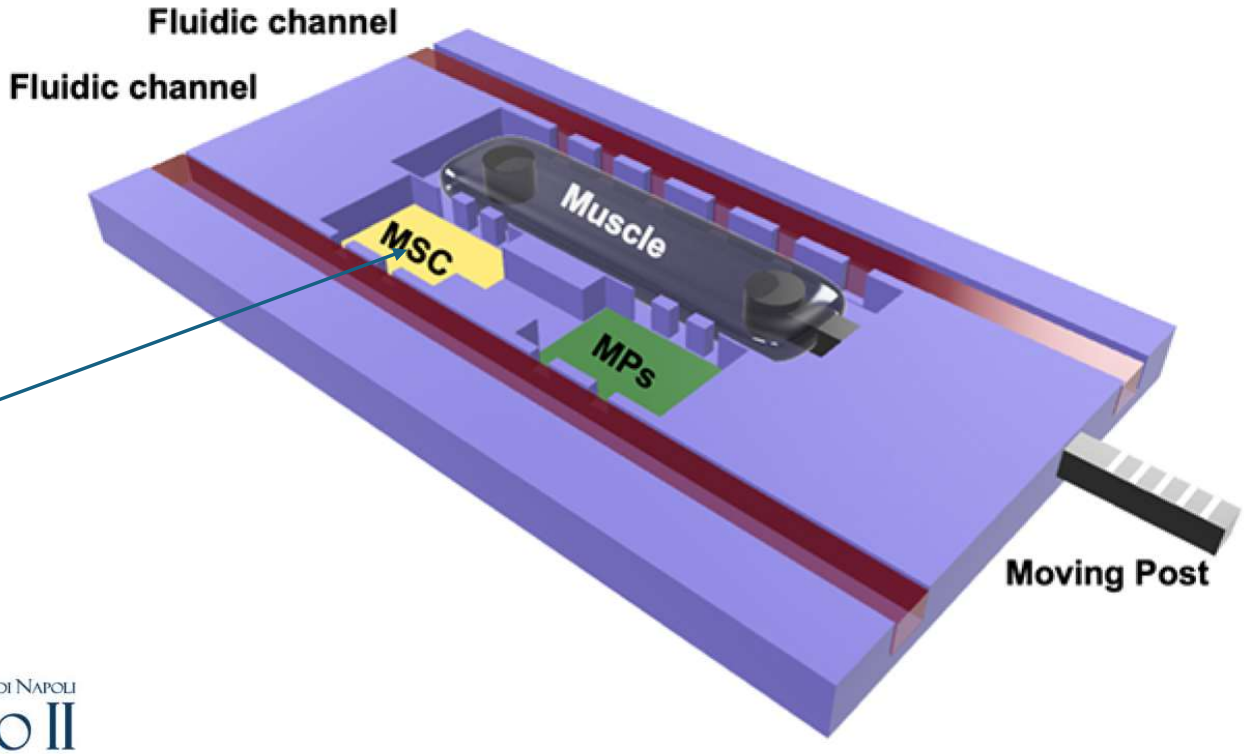


# Organ Chip device for FOP




**From our group**

**C2C12_ACVR1_wt**
**C2C12_ACVR1_R206H**

**C3H10T1/2_wt**
**C3H10T1/2_R206H**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