Panoramica sulle recenti ricerche

Updates on key Research themes in FOP

Renata Bocciardi

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

UNIVERSITÀ DEGLI STUDI DI GENOVA

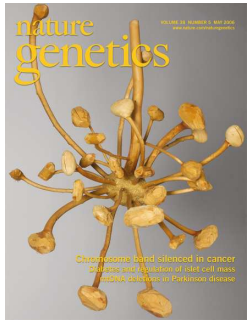
DINOGMI

GASLINI

The first critical step: the diagnosis

Diagnosis → **Natural history of the disease** → **Genetic cause** → **Pathological mechanisms** → **Therapies**

Castello di Avio (TN)



2006

The FOP Gene found

Genetics in Medicine (2022) 24, 2422–2433

Genetics in Medicine
An Official Journal of the ACMG

ELSEVIER

www.journals.elsevier.com/genetics-in-medicine

ARTICLE

The natural history of fibrodysplasia ossificans progressiva: A prospective, global 36-month study

Robert J. Pignolo[1,*], Geneviève Baujat[2], Matthew A. Brown[3,4], Carmen De Cunto[5], Edward C. Hsiao[6], Richard Keen[7], Mona Al Mukaddam[8], Kim-Hanh Le Quan Sang[2], Amy Wilson[9], Rose Marino[9], Andrew Strahs[9], Frederick S. Kaplan[6,*]

2014–2016:
FOP Global Natural History Study

2017

The world's first clinical trial using a drug candidate identified through FOP **iPS cells** (reprogrammed patient cells)
Kyoto University Hospital

Journal of Bone and Mineral Research, 2024, **39**, 382–398
https://doi.org/10.1093/jbmr/zjae029
Advance access publication: February 16, 2024
Research Article

ASBMR The American Society for Bone and Mineral Research

OXFORD

Matrix metalloproteinase-9 deficiency confers resilience in fibrodysplasia ossificans progressiva in a man and mice

Vitali Lounev[1,2], Jay C. Groppe[3], Niambi Brewer[1,2], Kelly L. Wentworth[4,5], Victoria Smith[6], Meiqi Xu[1,2], Lutz Schomburg[7], Pankaj Bhargava[6], Mona Al Mukaddam[1,2,8], Edward C. Hsiao[5,9], Eileen M. Shore[1,2,10], Robert J. Pignolo[11,†], Frederick S. Kaplan[1,2,8,†,*]

2017

Identification of FAPs as the Progenitor Cells

2024

Genetic Modifiers

Diagnosis | **Genetic cause** | **Natural history of the disease** | **Pathological mechanisms** | **Therapies**

2009

European Journal of Human Genetics (2009) 17, 311 – 318
© 2009 Macmillan Publishers Limited All rights reserved 1018-4813/09 $32.00
www.nature.com/ejhg

ARTICLE

Mutational analysis of the *ACVR1* gene in Italian patients affected with fibrodysplasia ossificans progressiva: confirmations and advancements

Renata Bocciardi[1], Domenico Bordo[2], Marco Di Duca[3], Maja Di Rocco[4] and Roberto Ravazzolo[*,1,5]

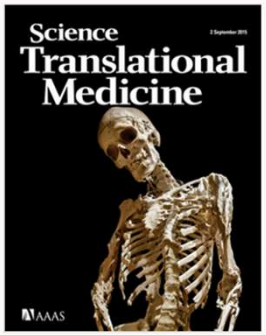
[1]*Laboratory of Molecular Genetics, G Gaslini Institute, Genova, Italy;* [2]*National Cancer Research Institute, Genova, Italy;* [3]*Laboratory on Pathophysiology of Uremia, G Gaslini Institute, Genova, Italy;* [4]*Second Unit of Pediatrics, G Gaslini Institute, Genova, Italy;* [5]*Department of Pediatric Sciences 'G. de Toni' and CEBR, University of Genova, Genova, Italy*

2010–2011

Identification of RARγ Agonists (Palovarotene)

2015

Discovery of Activin A as the "Culprit Ligand"



When muscle turns to bone

Aris Economides
Regeneron
Terrytown, New York (USA)

PNAS

Junia Toguchida
Kyoto University
Kyoto, Japan

2020s: Clinical Trials

Garetosmab (an anti-Activin A antibody) Regeneron Pharmaceuticals announced that the U.S. Food and Drug Administration has accepted for **Priority Review the Biologics License Application (BLA)** for garetosmab

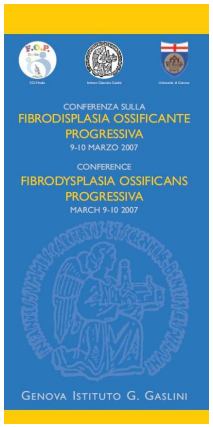
Saracatinib (an oral kinase inhibitor repurposed from cancer research to target the ACVR1 kinase activity).

2023: First FDA-Approved Treatment In August

2023, the U.S. FDA approved **Palovarotene** (**Sohonos**)

INC000928/Zilurgisertib

Andecaliximab



2007
1° Congresso FOP (Genova)

2009
3° Congresso FOP (Cerignola, FG)

2011
5° Congresso FOP (Roma)

2013
7° Congresso FOP (Parma)

2015
9° Congresso FOP (Roma)

2008
2° Congresso FOP (Rovereto,TN)

2010
4° Congresso FOP (Verbania)

2012
6° Congresso FOP (Milano)

2014
8° Congresso FOP (Genova)

2016

10° Congresso FOP
(Livorno)

12° MEETING FOP ITALIA
INCONTRO CON I PAZIENTI E LE FAMIGLIE
NAPOLI - 6 OTTOBRE 2018
NH Ambassador - Via Medina 70

2018

12° Congresso FOP
(Napoli)

NH TORINO

2020

14° Congresso FOP
(OnLine)

2017

11° Congresso FOP
DDF
(Alghero)

2019

13° Congresso FOP
(San Marino)

13° MEETING FOP ITALIA
INCONTRO CON I PAZIENTI E LE FAMIGLIE
SAN MARINO - 30 novembre 2019
Grand Hotel Primavera
via L.Cibrario 24
47893 Borgo Maggiore (RSM)

20

15° Congr
(Lec

con il patro
FONDAZ

15° MEETI
INCONTRO CON I PA
LECCE - 15
Mercure Hote
via A.Salandra 6

Gene therapy

15.50 **L'evoluzione del panorama terapeutico per la FOP**
The Evolving Therapy Landscape for FOP
Mark Hamilton (IFOPA, USA)

15.10 **Aggiornamenti sulla ricerca**
Research Updates
Paul Yu (Harvard Medical School, Boston)

14.30 **Comprendere la FOP. Un viaggio eccitante**
Understanding FOP - An Exciting Journey
Eileen Shore (University of Pennsylvania, Philadelphia)

Anti-ActA antibodies

14.50 **Attivina A come bersaglio terapeutico per la FOP**
Activin A as a therapeutic target in FOP
Aris Economides (Regeneron Pharmaceuticals, Inc.)

ECM & Proteases

16:50 **Andecal**
Deborah Wengher (Ashibio Inc., California, USA)

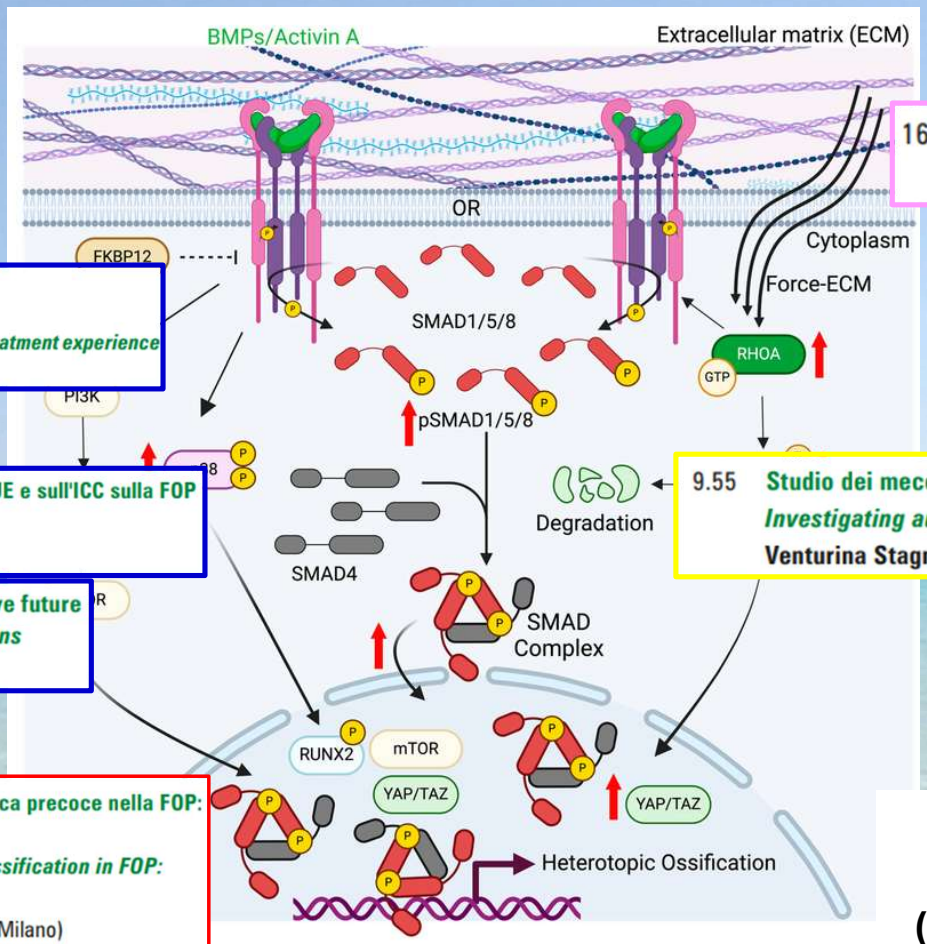
Kinase inhibitors

11.45 **Tofacitinib nel trattamento della FOP: revisione della letteratura ed esperienza personale di trattamento**
Tofacitinib in the treatment of FOP: literature review and personal treatment experience
Irene Bruno (IRCCS Burlo Garofolo, Trieste)

12.00 **Incyte Biosciences Italy**

12.15 **Aggiornamento sulla sperimentazione STOPFOP finanziata dall'UE e sull'ICC sulla FOP**
Update on the EU-funded STOPFOP trial and the ICC on FOP
Marelise Eekhoff (VU University Medical Center, Amsterdam)

15.30 **Inibitori della chinasi ACVR1/ALK2 per la FOP e prospettive future**
ACVR1/ALK2 kinase inhibitors for FOP and future directions
Alex Bullock (University of Oxford)



Microenvironment, Hypoxia, autophagy

9.55 **Studio dei meccanismi di (ri)attivazione dell'autofagia per contrastare la FOP**
Investigating autophagy (re)activation mechanisms to counteract FOP
Venturina Stagni (Istituto di Biologia e Patologia Molecolari -IBPM-Roma)

Inflammation

9.35 **Interazioni macrofagi-FAP nell'ossificazione eterotopica precoce nella FOP: il ruolo emergente della SPP1**
Macrophage–FAP interactions in early heterotopic ossification in FOP: the emerging role of SPP1
Silvia Brunelli (Università degli studi di Milano Bicocca, Milano)

10.15 **FOP news**
Riccardo Papa (Istituto G. Gaslini, Genova)

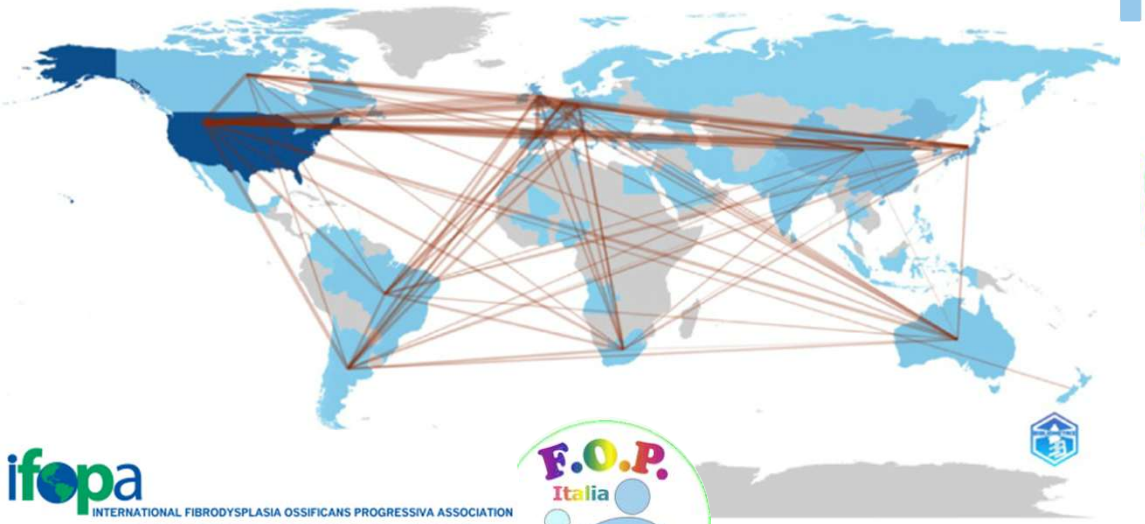
Endochondral bone neoformation (inhibitors of differentiation - Palovarotene)

FIBRODISPLASIA OSSIFICANTE PROGRESSIVA

20°

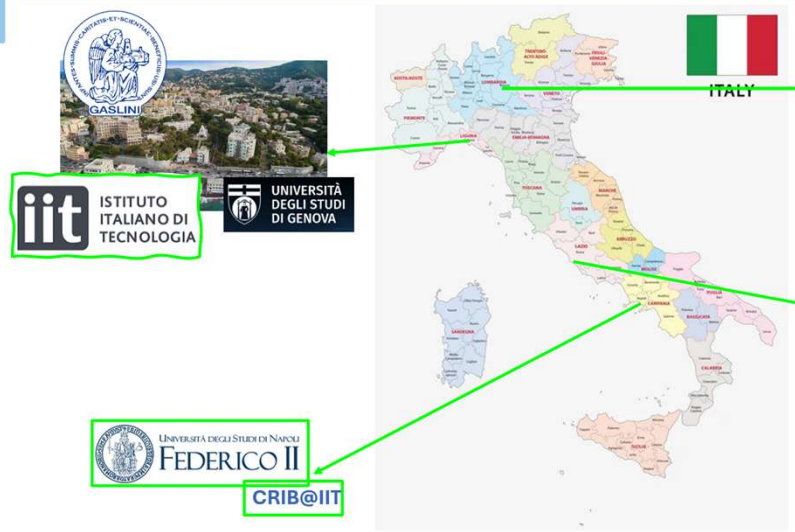
FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

18° MEETING FOP ITALIA ODV



ifopa
INTERNATIONAL FIBRODYSPLASIA OSSIFICANS PROGRESSIVA ASSOCIATION
FUND RESEARCH, FIND A CURE, SUPPORT FAMILIES ... WORLDWIDE

F.O.P. Italia ONLUS



Activation of PPARγ redirects fibro-adipogenic progenitors to replace ectopic bone with fat in models of fibrodysplasia ossificans progressiva and trauma-induced heterotopic ossification

Authors: Pratik Koirala[1], Ziyu Chen[1,2], Sam Siegel[1], Chang Liu[1], Zachary Williams[1], Mishina[4], Vicki Rosen[3], Shailesh Agarwal[1]*

A closed-loop cell therapy engineered to autonomously secrete Activin A inhibitor protects from fibrodysplasia ossificans progressiva

Authors: Pratik Koirala[1]·#, PhD; Ziyu Chen[1]·#, MD; Mengfan Wu[1], MD; David Maridas[2], PhD; Ashley Siegel[1], MD; Chang Liu[1], Samerender Hanumantharao[1], PhD; Yuji Mishina[3], PhD; Vicki Rosen[2], PhD; Shailesh Agarwal[1]·*, MD

nature communications

Article

https://doi.org/10.1038/s41467-026-68857-8

Early detection of aberrant cell fate and repair using circulating progenitor cells in patients with heterotopic ossification

Received: 17 May 2024
Accepted: 19 January 2026
Published online: 31 January 2026
Check for updates

Johanna Nunez[1], Matilda Holtz[2,3], Sneha Korlakunta[1], Hanil Kang[2,3], Florence Lin[2,3], Hannah Stowe[2,3], Chase A. Pagani[1], Achira Shah[1], Elise C. Jeffery[1], Meriam Elhamad[1], Saeed Nazemidashtarjandi[2,3], Robert Tower[1], Ji Hae Choi[1], Heeseog Kang[1], Alexandra Callan[4], Antonia F. Chen[4], Cenk Ayata[5], Mehmet Toner[2,3], Benjamin Levi[1] & N. Murat Karabacak[2,3]

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

Do you remember Rosiglitazone?

Once upon a time in 2010...

CASE REPORT

JBMR

Rosiglitazone Therapy Is Associated with Major Clinical Improvements in a Patient with Fibrodysplasia Ossificans Progressiva

Davide Gatti, Ombretta Viapiana, Maurizio Rossini, and Adami Silvano
University of Verona, Rheumatology Unit, Valeggio, Verona, Italy

ABSTRACT
Fibrodysplasia ossificans progressiva (FOP) is a rare genetic condition characterized by progressive heterotopic ossification, increasing disability, and cumulative immobility. Thiazolidinediones, introduced in 1999 for the treatment of diabetes, enhance bone marrow adipogenesis at the expense of new bone formation, and this might be exploited for the treatment of FOP. A 48-year-old woman with severe FOP characterized by continuous flares that she was partially controlling only with high prednisone doses was given rosiglitazone (initially 4 mg and then 8 mg daily) for 14 months. No new flare-ups were observed during rosiglitazone therapy as compared to the five episodes observed during the previous year while on 20 to 25 mg prednisone daily. The steroid dose could be lowered progressively to 5 mg/day, the skin became softer, and the articular mobility improved impressively. This case report seems to suggest that rosiglitazone therapy, possibly in association with small doses of prednisone, is associated with important clinical improvements in patients with FOP.

Hindawi Publishing Corporation
PPAR Research
Volume 2010, Article ID 541927, 7 pages
doi:10.1155/2010/541927

Review Article

Is There a Biological Basis for Treatment of Fibrodysplasia Ossificans Progressiva with Rosiglitazone? Potential Benefits and Undesired Effects

Renata Bocciardi[1] and Roberto Ravazzolo[1,2]

[1] *Molecular Genetics Unit, G. Gaslini Institute, 16147 Genova, Italy*
[2] *Department of Pediatrics, Center of Excellence for Biomedical Research (CEBR), University of Genova, 16147 Genova, Italy*

COMMENTARY

JBMR

Viewing FOP Through Rosi-Colored Glasses

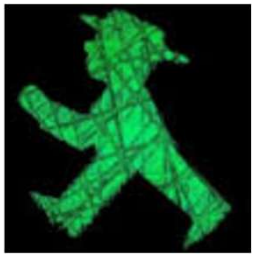
Frederick S Kaplan,[1,2] Robert J Pignolo,[1,2] and Eileen M Shore[1,3]
[1]Departments of Orthopaedic Surgery, Medicine,[2] and Genetics,[3] University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Rosiglitazone & FOP

Review Article

Hindawi Publishing Corporation
PPAR Research
Volume 2010, Article ID 541927, 7 pages
doi:10.1155/2010/541927

Is There a Biological Basis for Treatment of Fibrodysplasia Ossificans Progressiva with Rosiglitazone? Potential Benefits and Undesired Effects



Renata Bocciardi[1] and Roberto Ravazzolo[1,2]

[1] *Molecular Genetics Unit, G. Gaslini Institute, 16147 Genova, Italy*
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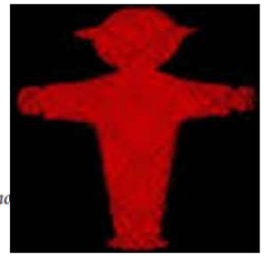
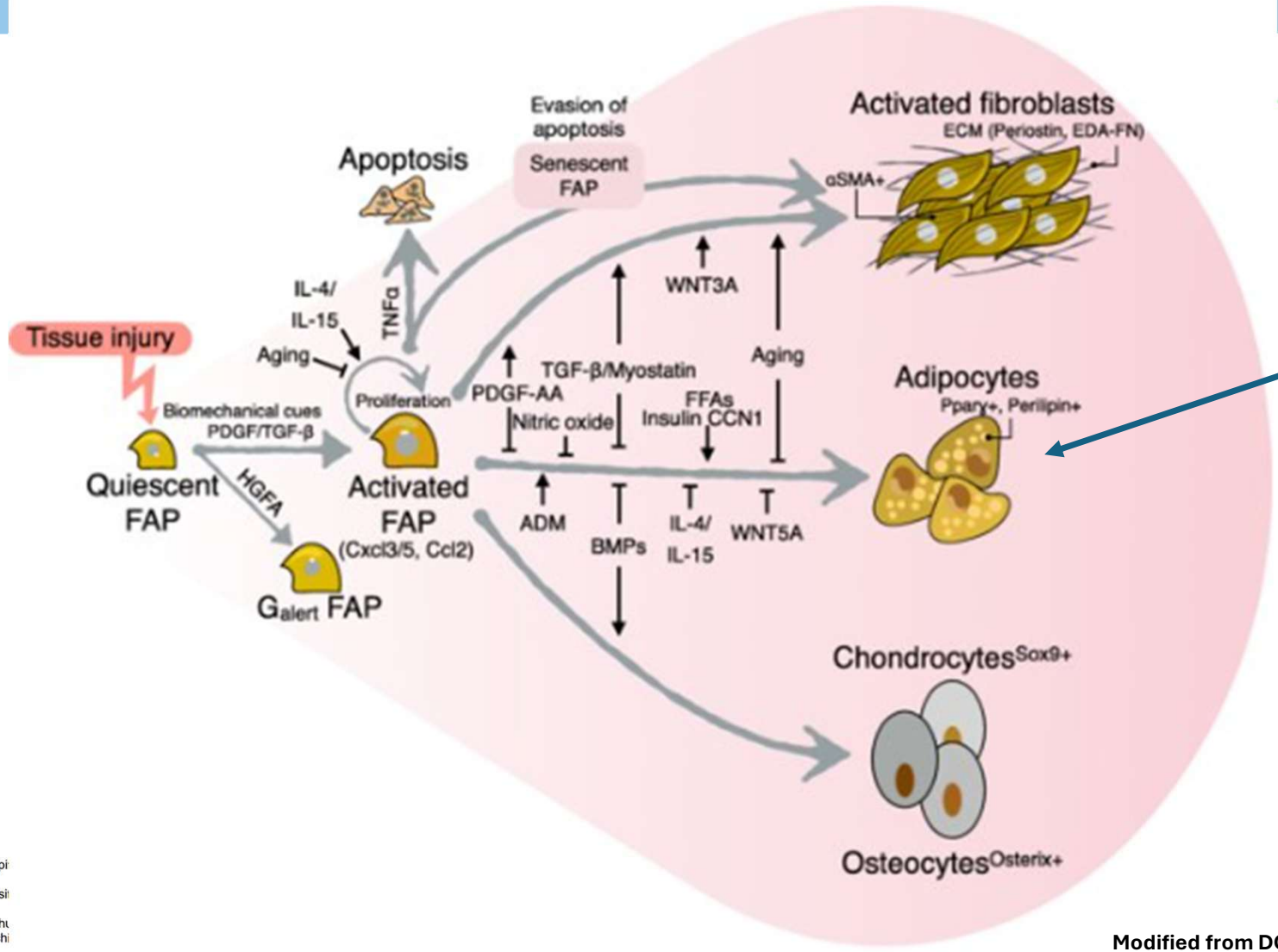


- **ROSI (in generale i farmaci TZD è un forte attivatore di PPAR-γ**
- **PPAR-γ ha un potente effetto anti-infiammatorio**
- **PPAR-γ ha un effetto significativo sul differenziamento orientando verso l'adipogenesi rispetto all'osteogenesi**

- **ROSI può avere effetti collaterali**
- **Sono necessari studi clinici strutturati**

Activation of PPARγ redirects fibro-adipogenic progenitors to replace ectopic bone with fat in models of fibrodysplasia ossificans progressiva and trauma-induced heterotopic ossification

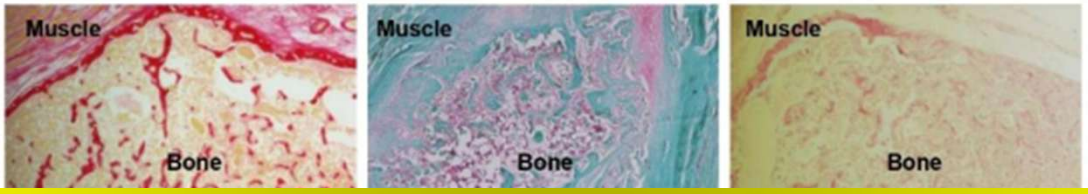


PPARγ+ Adipociti

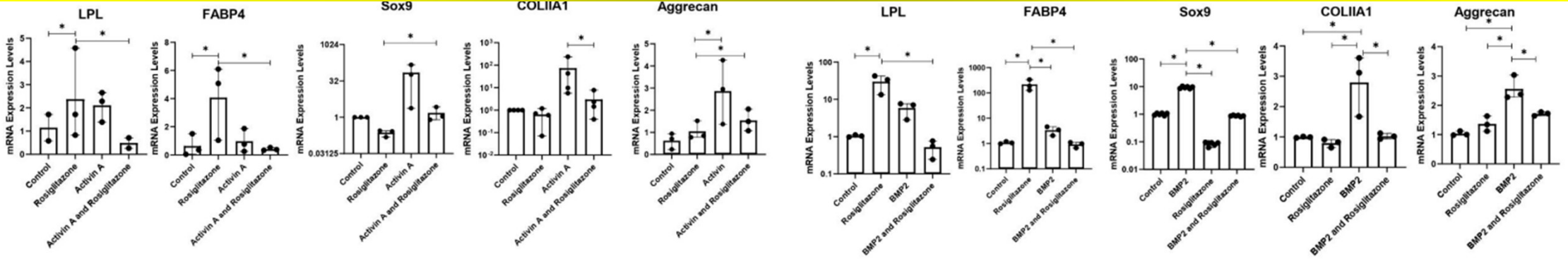
Affiliations:
[1]Department of Surgery, Brigham and Women's Hospi
Boston, Massachusetts, USA.
[2]Department of Bone and Joint Surgery, Peking Universi
Guangdong, China.
[3] Harvard School of Dental Medicine, Boston, Massachu
[4] University of Michigan Dental School, Ann Arbor, Michi

Modified from DOI: 10.1186/s13395-021-00265-6

FOP lesions do not contain adipocytes or adipogenic signals

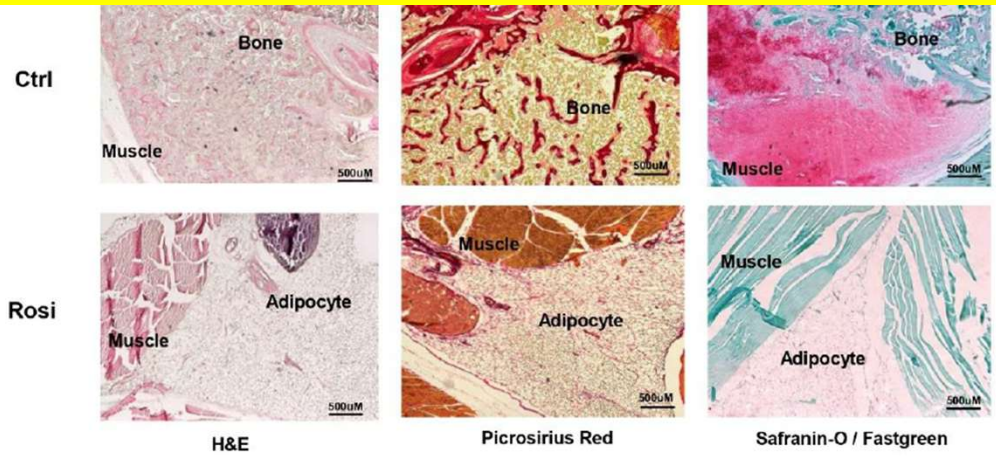


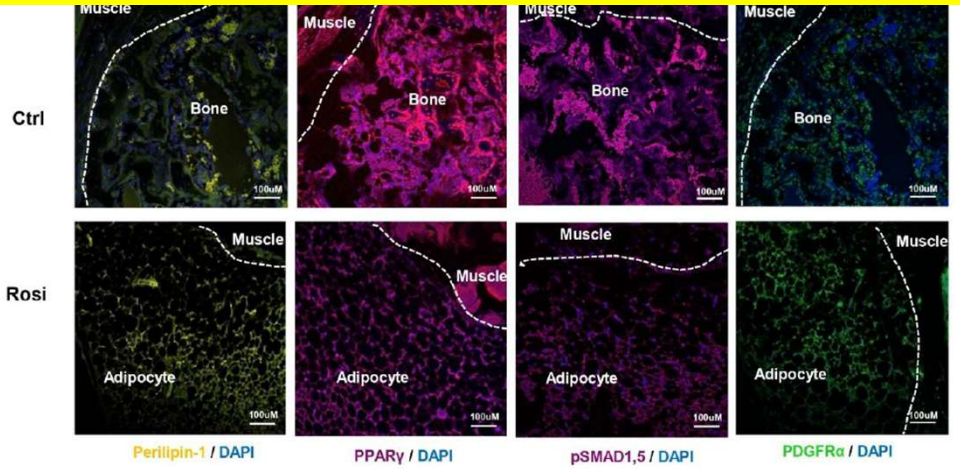
Il trattamento con ROSI nei topi FOP inibisce la formazione di osso ectopico e induce la produzione di tessuto adiposo



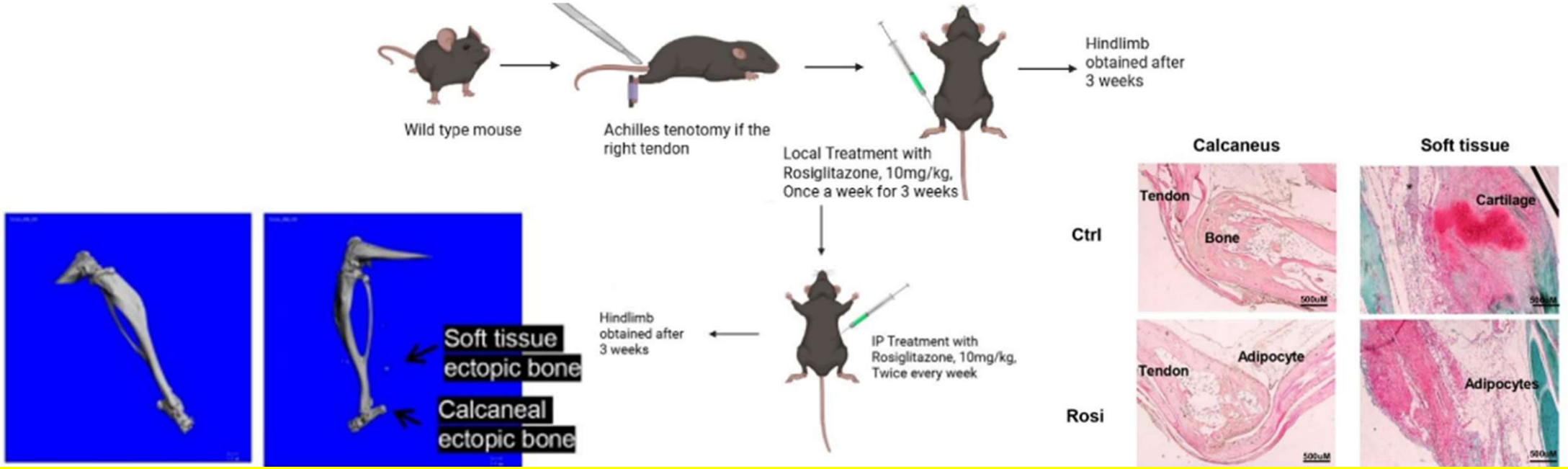
Treatment with rosiglitazone significantly reduces formation of post-injury FOP lesions

Il trattamento con ROSI nei topi FOP riduce in maniera significativa la formazione di osso ectopico



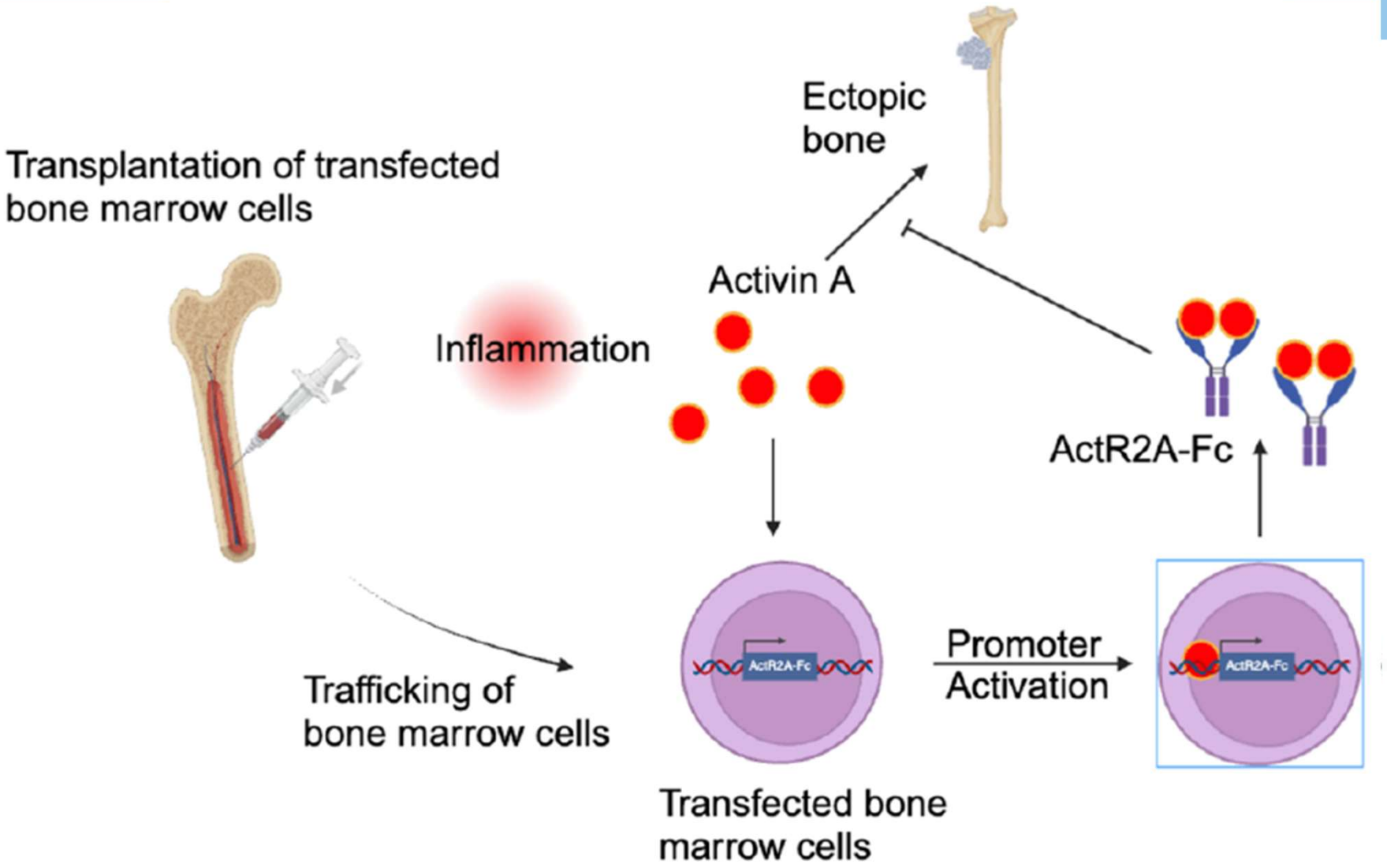


Both Systemic and local treatment with rosiglitazone reduces heterotopic bone formation in a trauma-induced HO model



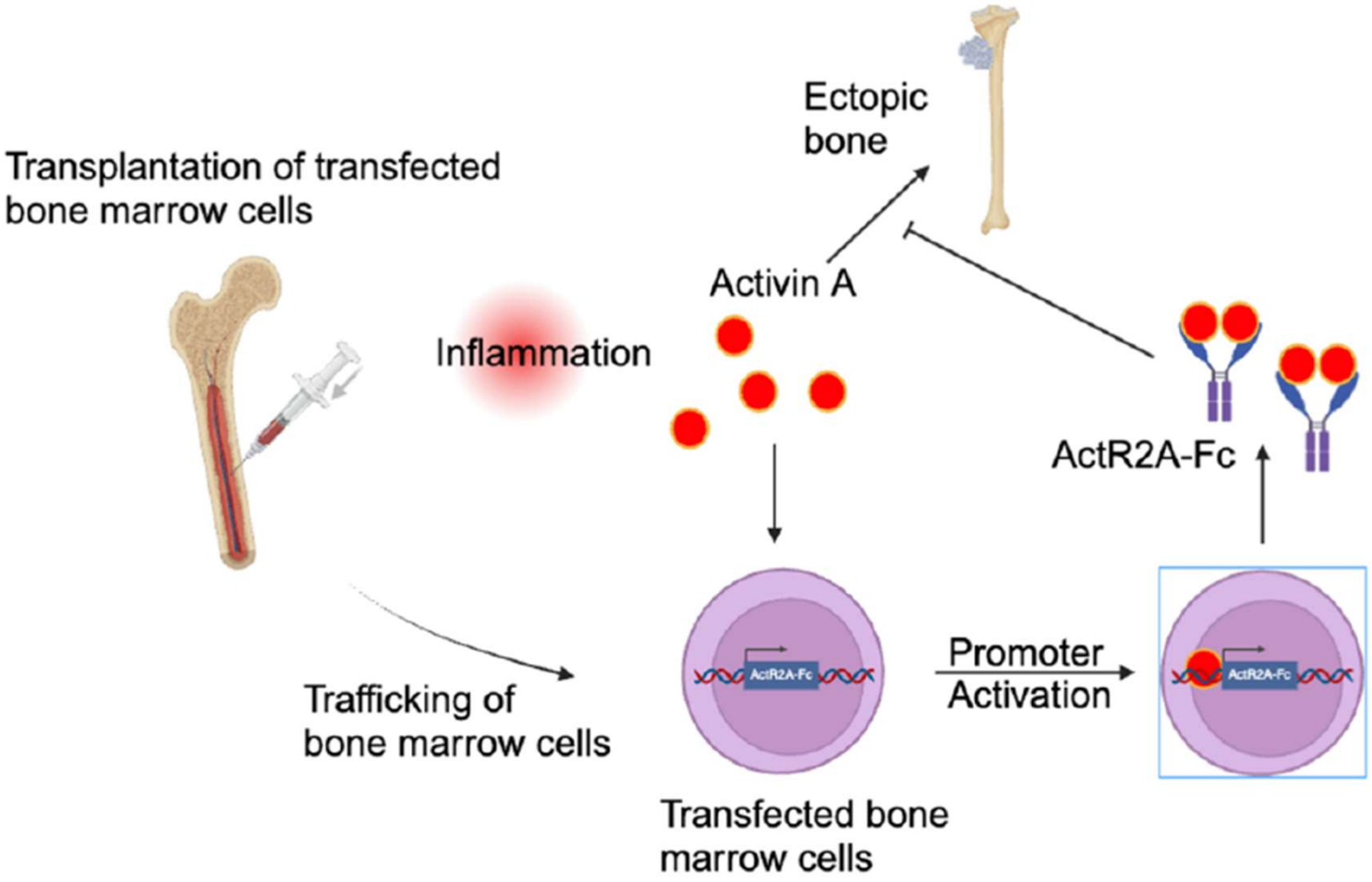
Il trattamento con ROSI riduce la formazione di osso ectopico anche in un modello di HO post-traumatica ed è efficace sia somministrato localmente che per via generale

A closed-loop cell therapy engineered to autonomously secrete Activin A inhibitor protects from fibrodysplasia ossificans progressiva

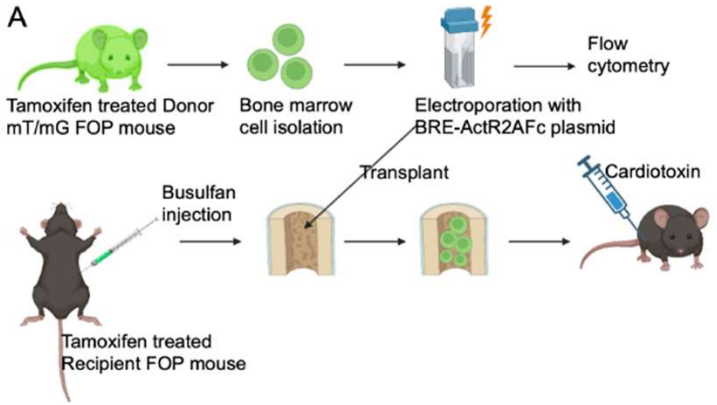


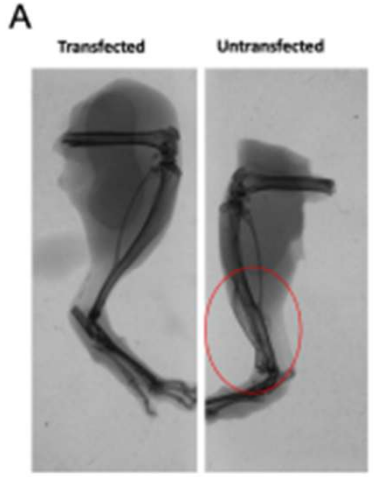
A closed-loop cell therapy engineered to autonomously secrete Activin A inhibitor protects from fibrodysplasia ossificans progressiva

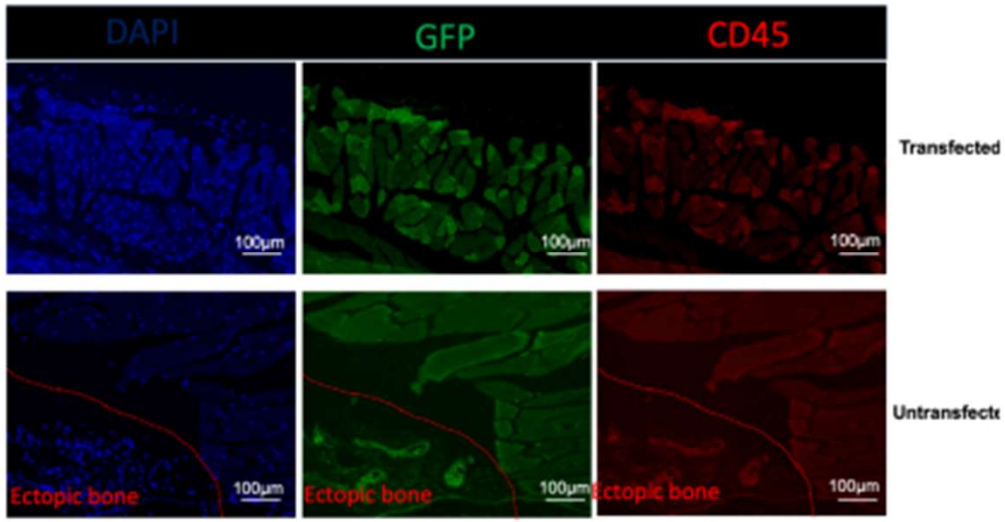
Authors: Pratik Koirala[1·#], PhD; Ziyu Chen[1·#], MD; Mengfan Wu[1], MD; David Maridas[2], PhD; Ashley Siegel[1], MD; Chang Liu[1], Samerender Hanumantharao[1], PhD; Yuji Mishina[3], PhD; Vicki Rosen[2], PhD; Shailesh Agarwal[1·*], MD

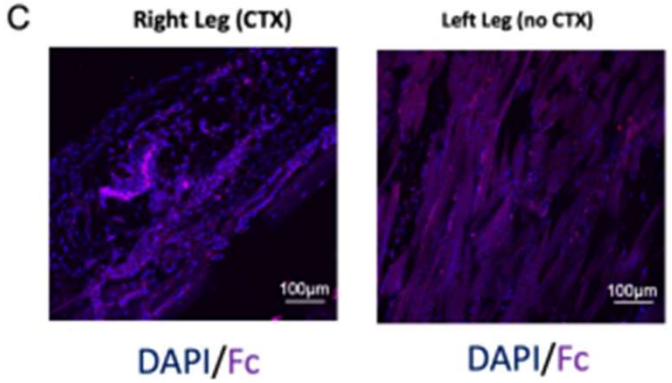


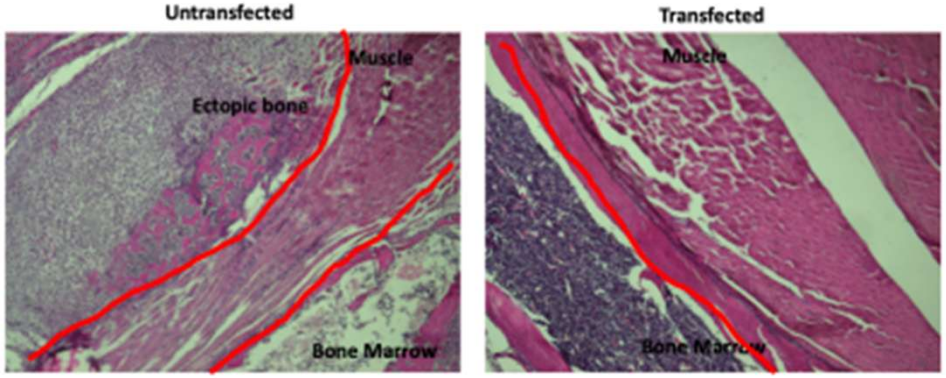
Effect of transplanted bone marrow cells 56 days post CTX injection











Closed-loop strategy targeting Activin A

In this study the authors describe the development of an autologous, closed-loop cell therapy which can migrate to sites of tissue injury and locally secreting an inhibitor of Activin A.

Through our use of an Activin A-responsive promoter to drive expression of the recombinant Activin A inhibitor, this engineered cell therapy exhibits closed-loop behavior and effectively prevents heterotopic bone formation in a mouse model of fibrodysplasia ossificans progressiva (FOP).

This approach may be impactful beyond FOP and provide a blueprint for the development of marrow-derived cell therapies across the disease spectrum.

Questo studio descrive lo sviluppo di una terapia cellulare autologa capace di migrare nei siti di lesione e rilasciare localmente un inibitore di Activina A.

La terapia previene la formazione di osso eterotopico nel modello murino di FOP e offre un modello per nuove terapie cellulari del midollo osseo.

nature communications

Article

https://doi.org/10.1038/s41467-026-68857-8

Early detection of aberrant cell fate and repair using circulating progenitor cells in patients with heterotopic ossification

Received: 17 May 2024

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Check for updates

Johanna Nunez[1], Matilda Holtz[2,3], Sneha Korlakunta[1], Hanil Kang[2,3], Florence Lin[2,3], Hannah Stowe[2,3], Chase A. Pagani[1], Achira Shah[1], Elise C. Jeffery[1], Meriam Elhamad[1], Saeed Nazemidashtarjandi[2,3], Robert Tower[1], Ji Hae Choi[1], Heeseog Kang[1], Alexandra Callan[4], Antonia F. Chen[4], Cenk Ayata[5], Mehmet Toner[2,3], Benjamin Levi[1] & N. Murat Karabacak[2,3]

- Circulating mesenchymal progenitor cells (cMPCs) are isolated using a microfluidic iChip from patients undergoing hip replacement and a mouse model of traumatic HO, & exhibit HO-associated gene expression as early as 6 hours post-injury - 41 days before radiographic detection.

- RNA sequencing of cMPCs enabled development of a liquid biopsy-based HO risk prediction model, achieving up to 90% sensitivity and 100% specificity in human subjects.

- Furthermore, the model detected significant reductions in HO risk following prophylactic treatment, correlating with decreased HO volume. These findings establish a noninvasive platform for early detection and monitoring of HO and suggest broader utility for diseases involving aberrant mesenchymal cell fate.

- This approach enables high-throughput screening of at-risk patients and realtime assessment of therapeutic efficacy

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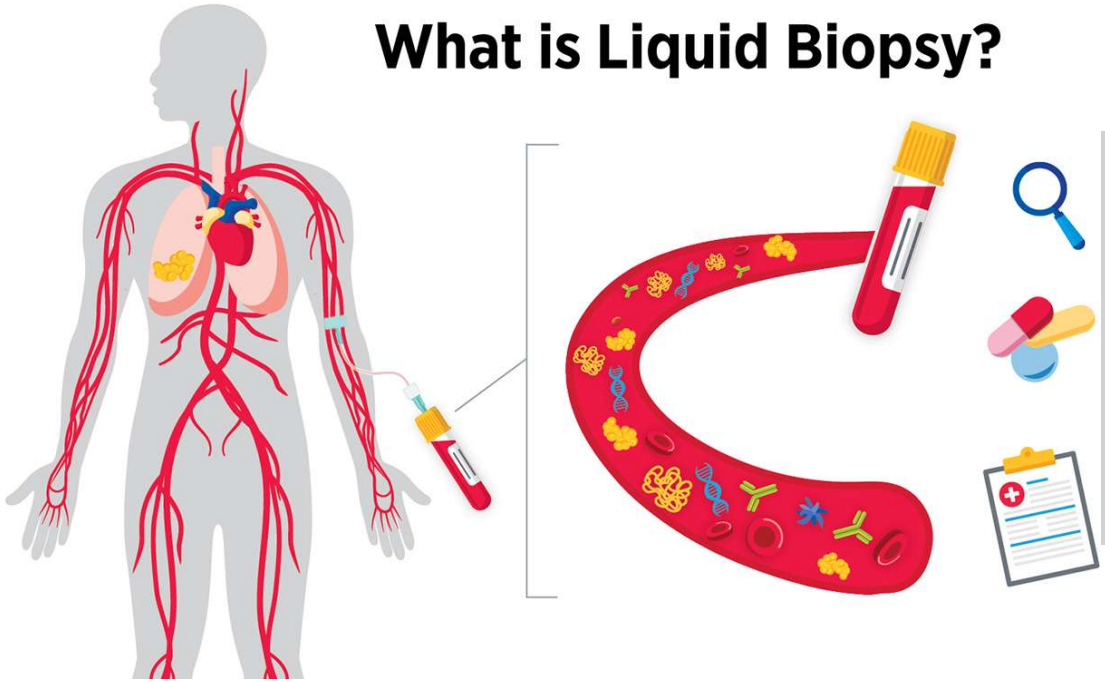
Article

https://doi.org/10.1038/s41467-026-68857-8

Early detection of aberrant cell fate and repair using circulating progenitor cells in patients with heterotopic ossification

What is Liquid Biopsy?



Modified from https://www.cancertodaymag.org/cancer-talk/what-is-liquid-biopsy/

Rilevare la presenza di cellule o acidi nucleici (DNA e RNA) derivanti da tumori o da profili di differenziamento tissutale specifico

- Ricavare firme molecolari specifiche per trattamenti personalizzati e per monitorarne l'efficacia

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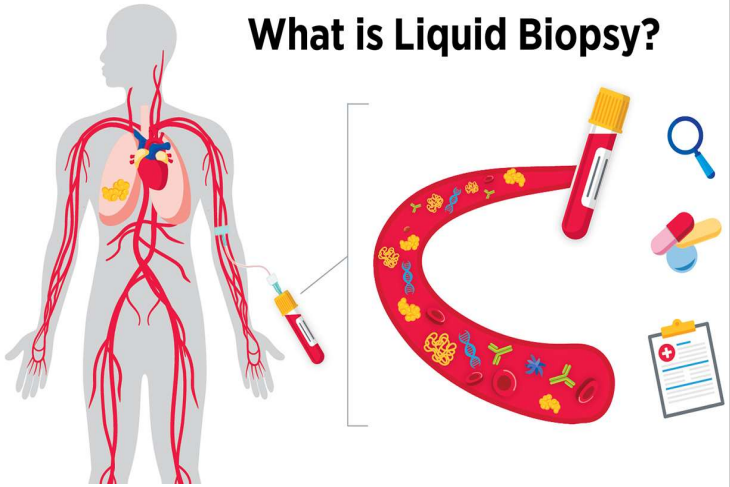
Article

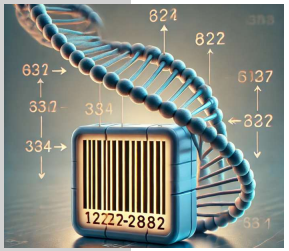
https://doi.org/10.1038/s41467-026-68857-8

Early detection of aberrant cell fate and repair using circulating progenitor cells in patients with heterotopic ossification



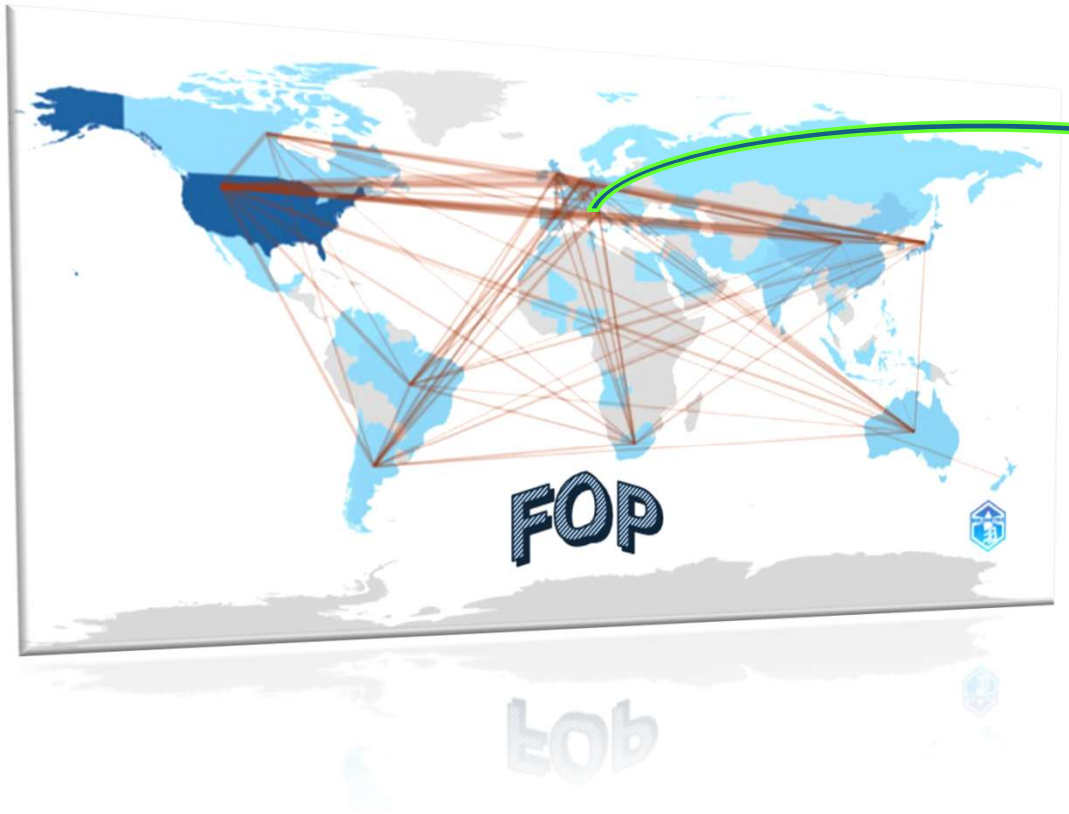
Modified from https://www.cancertodaymag.org/cancer-talk/what-is-liquid-biopsy/

- **Cellule mesenchimali progenitrici circolanti (6 ore post trauma/intervento fino a 41 giorni prima dell'evidenza radiografica di ossificazione ectopica) dopo trauma (topo) o intervento chirurgico (nell'uomo, protesi d'anca)**
- **Profilazione di queste cellule**
- **Generazione di un modello predittivo di ossificazione ectopica (90% specificità-100% sensibilità) basato sul codice a barre molecolare generato da questo studio**
- **Utile per predire la formazione di HO e per valutarne l'efficacia di trattamento**



Panoramica sulle recenti ricerche

Updates on key Research themes in FOP



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

Ministero dell'Università e della Ricerca

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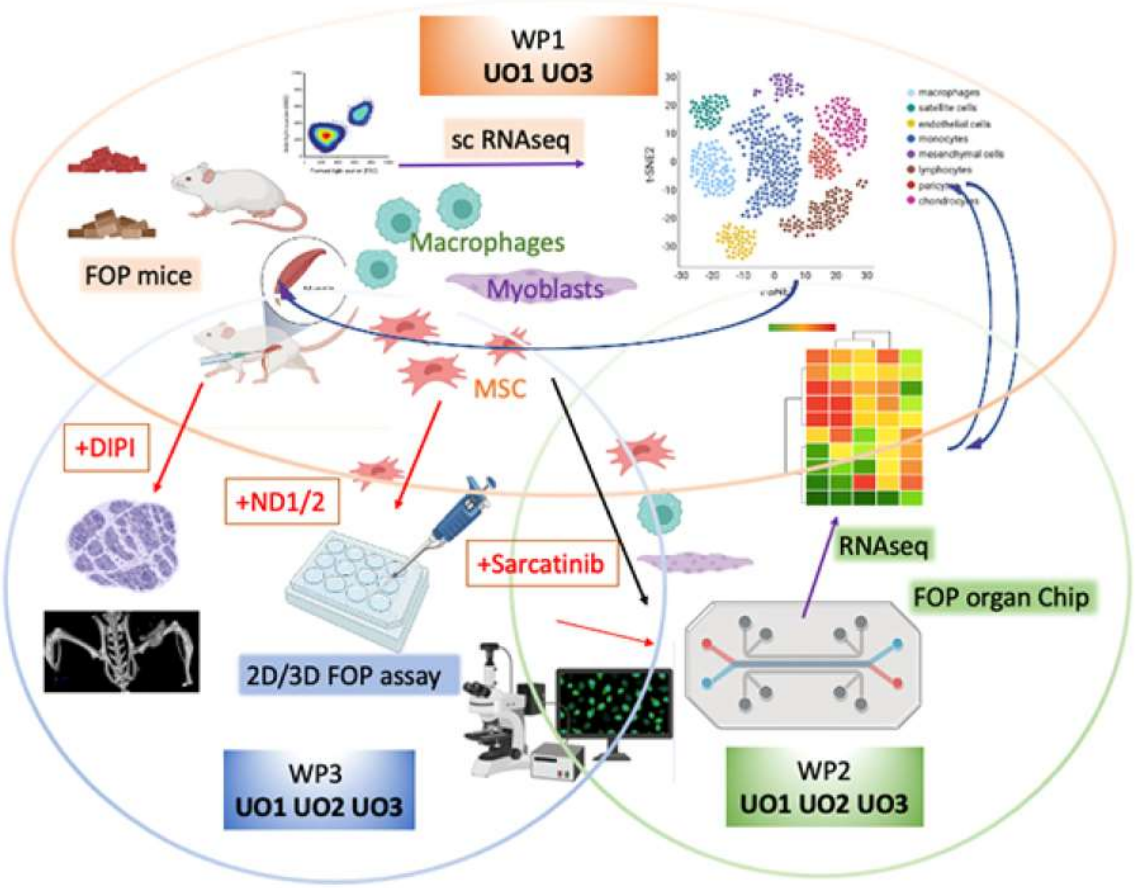
Prot. 2022TR9N4R

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



UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

UO1
Silvia Brunelli, PI
Responsabile Progetto
Riccardo Gamberale
Mauro Bergamaschi

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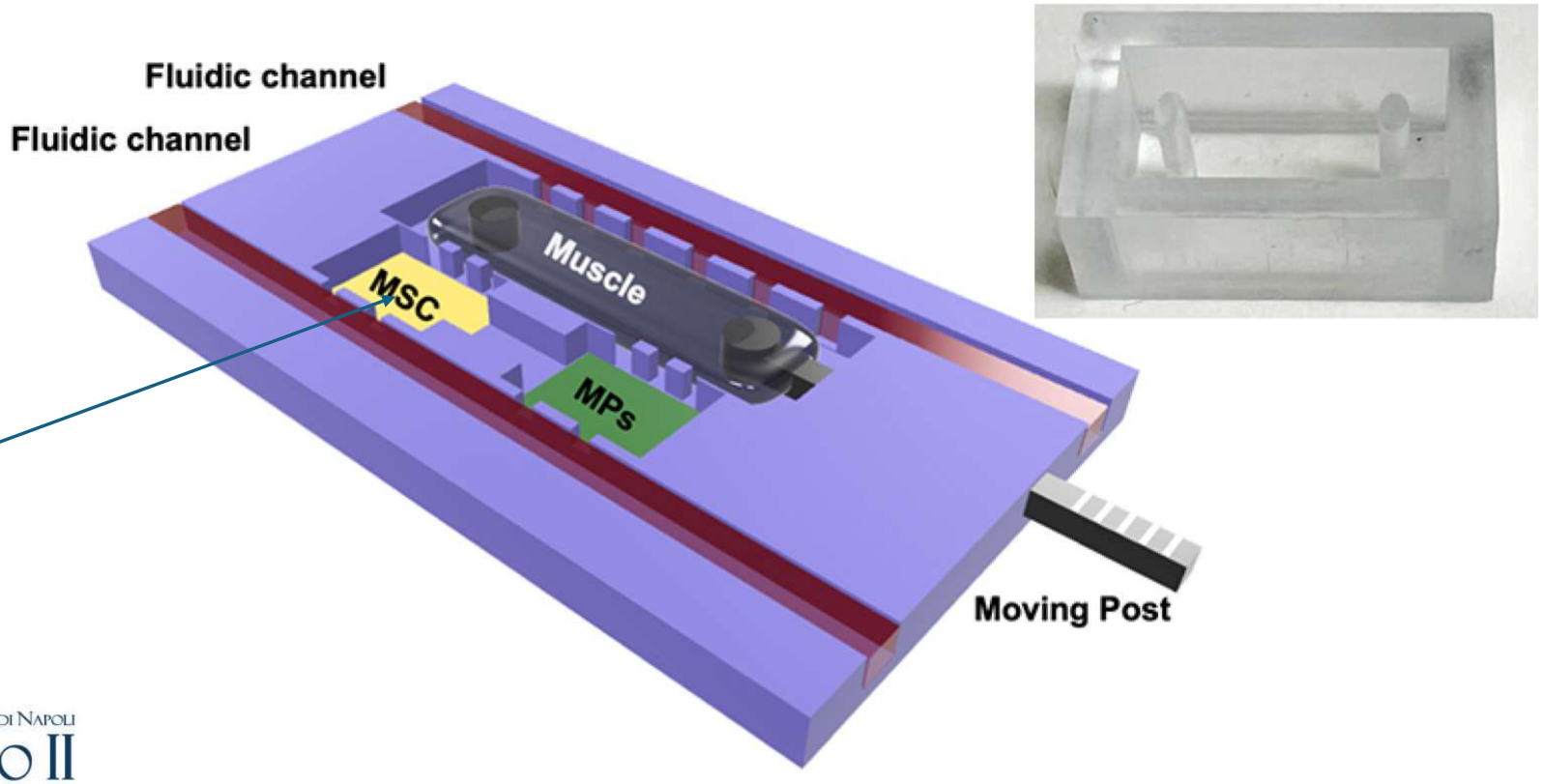
UO2
Paolo Netti
Francesco Urciuolo

UNIVERSITÀ DEGLI STUDI DI GENOVA

UO3
Renata Bocciardi
Serena Cappato
Michela Bellardita

Organ Chip device for FOP



From our group

C2C12_ACVR1_wt
C2C12_ACVR1_R206H

C3H10T1/2_wt
C3H10T1/2_R206H

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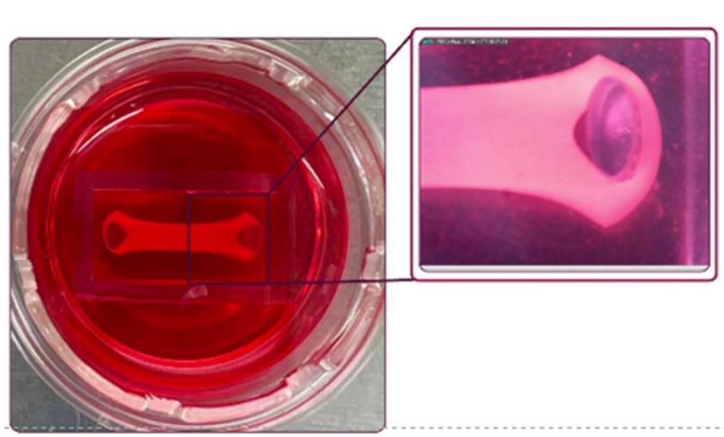
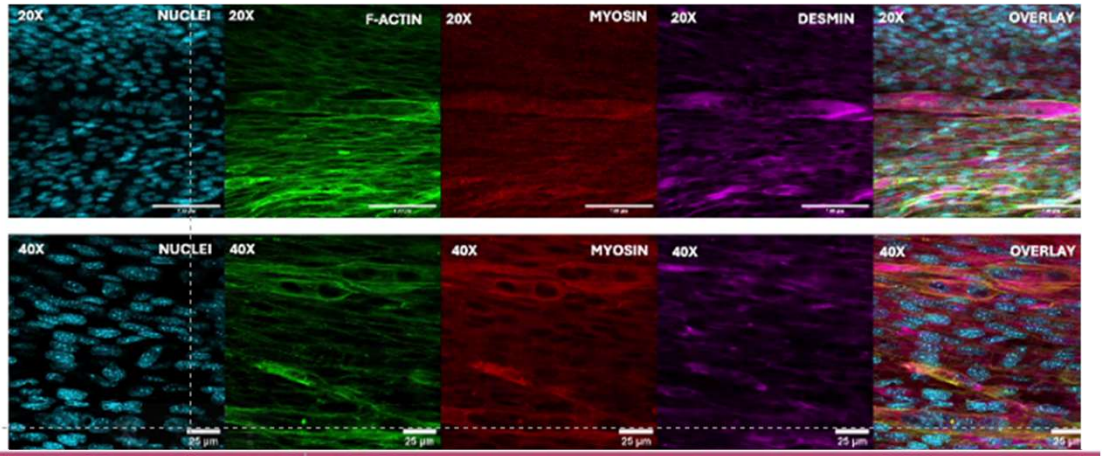
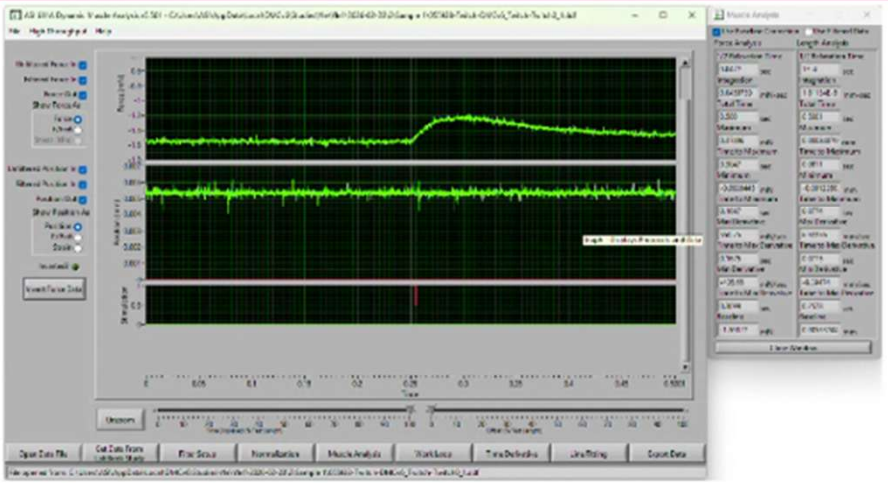
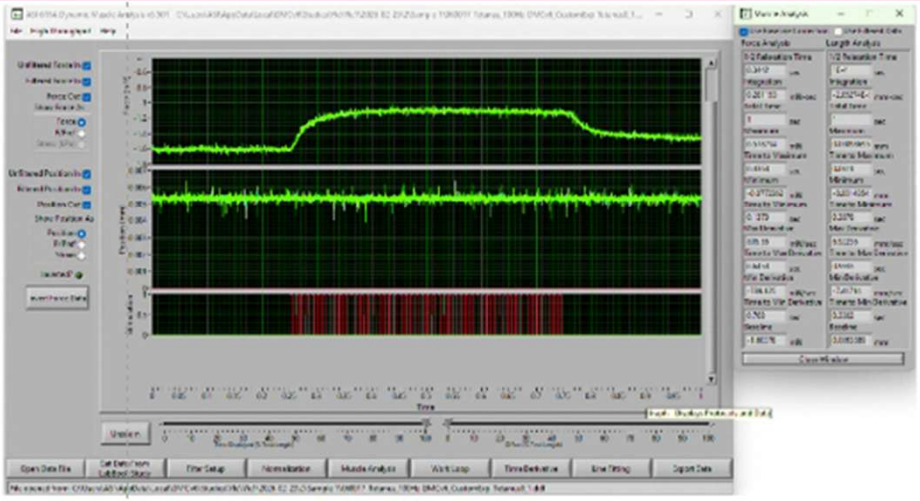
C2C12 3D model





Aurora: Electrical Stimuli 21 Days C2C12 Naples

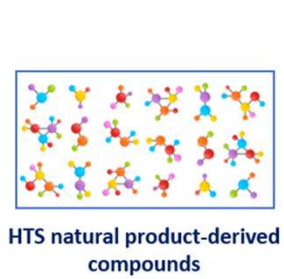


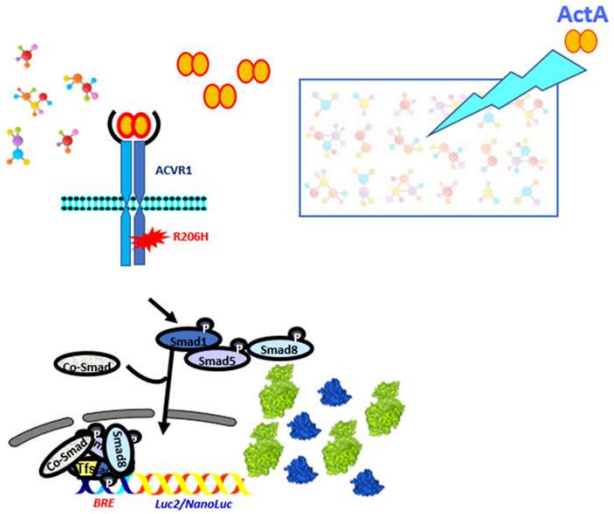


Screening of Natural product-derived compounds

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

√





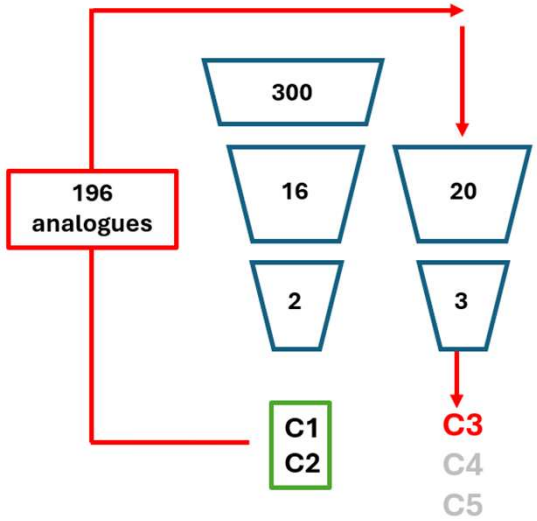
Confirmation:

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

√

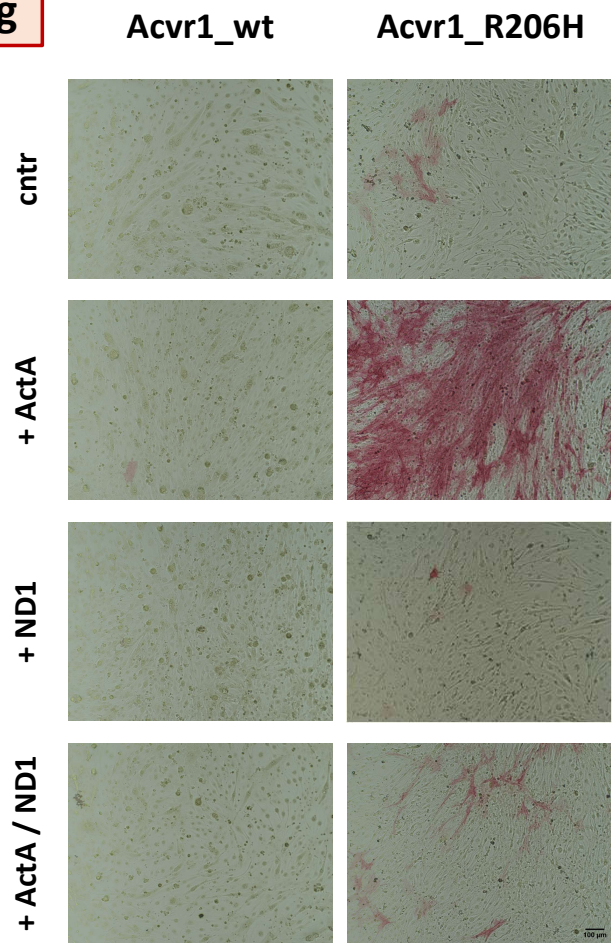
- ActA vs BMP2
- Effect on canonical and non canonical P-Smads
- *In vitro* differentiation (micromass cultures)
- Ex-vivo & In-vivo analysis (FOP mouse)

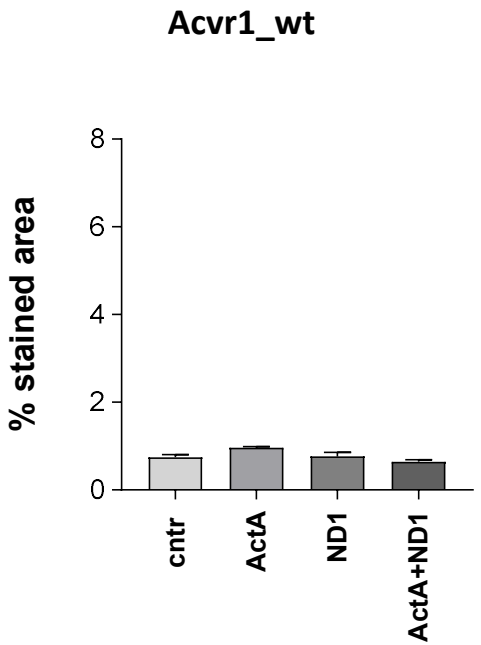
√

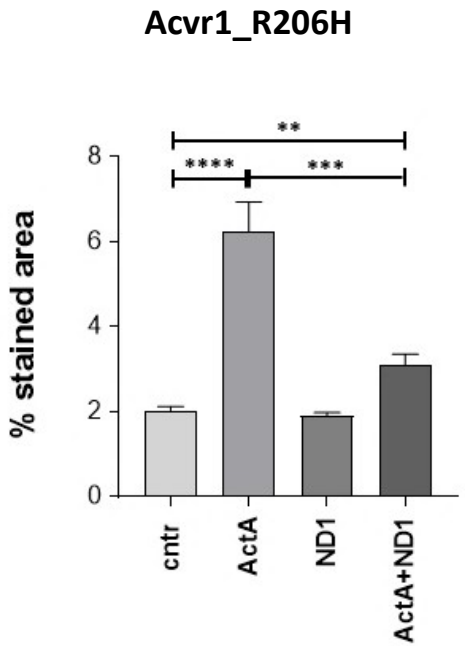


ND1 significantly reduces Activin A-induced mineralization in C2C12 Acvr1_R206H cells

ALP staining







**p ≤ 0,01; ***p ≤ 0,001; ****p ≤ 0,0001

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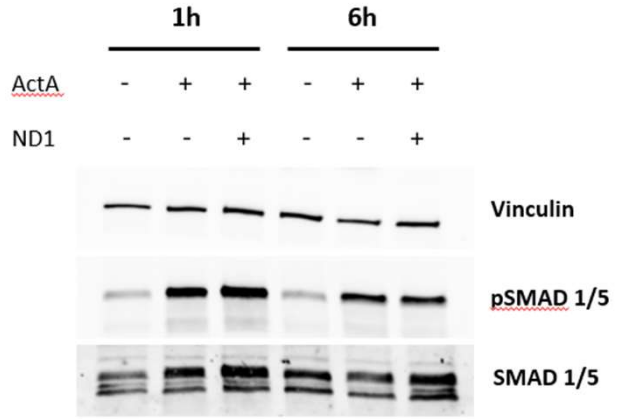
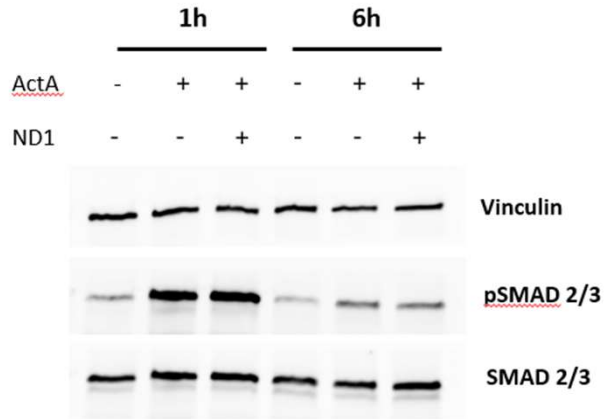
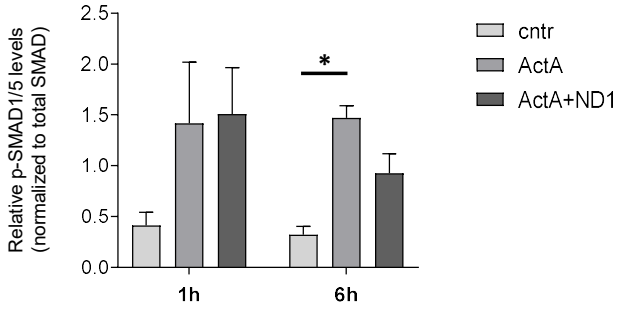
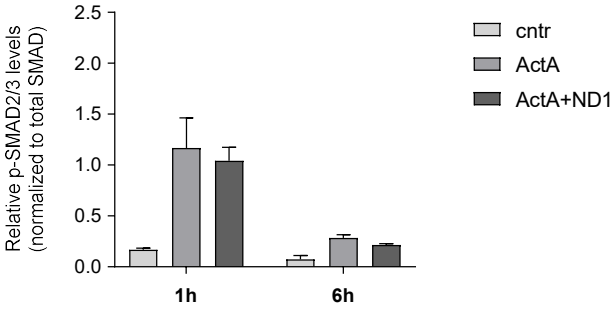
ND1 reduces Activin A-induced SMAD1/5 phosphorylation in C2C12 Acvr1_R206H cells









*p ≤ 0,05

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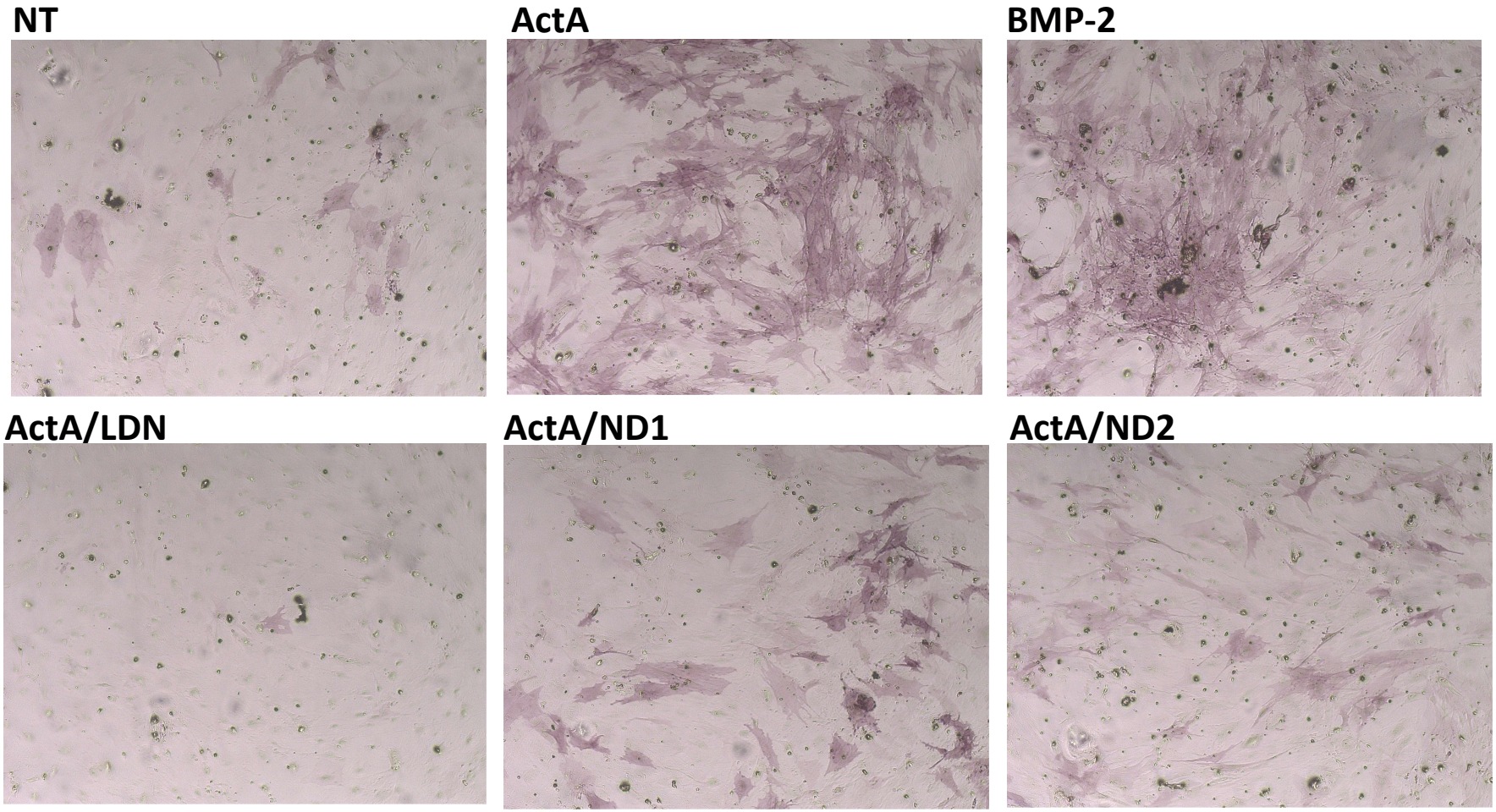
Effect of selected natural compound on osteogenic FAP_R206H differentiation



ALP staining

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Ministero della Salute

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