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MEETING SUMMARY
ASBMR 2021, HYBRID MEETING

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RARE BONE DISEASE HIGHLIGHTS FROM DAY 2

OCTOBER 2021

DISCLAIMER AND DISCLOSURES

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This content is supported by an independent educational grant from Ipsen, Kyowa Kirin and Ultragenyx.

Professor Dr Oliver Semler, MD has no disclosures to declare.

ENPP1

ENPP1: BACKGROUND

- Ectonucleotide pyrophosphatase/phosphodiesterase 1 **(ENPP1)** is a membrane-bound glycoprotein that **regulates bone mineralisation** by hydrolysing extracellular nucleotide triphosphates to produce pyrophosphate

- **ENPP1-deficiency results in either lethal arterial calcifications** (Generalised Arterial Calcification of Infancy, GACI), **phosphate wasting rickets, early onset osteoporosis, or progressive spinal rigidity** and a **50% lethality during infancy**
- Patients with moderate phenotypes can present with **rickets-like appearance on x-rays**

ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1

Kato K, et al. Proc Natl Acad Sci USA. 2012;109:16876-81 ; Maulding N, et al. Bone 2021;142:115656; Ferreira C, et al. J Bone Miner Res. 2021. DOI: 10.1002/jbmr.4418; Rutsch F. ASBMR 2021, Abstract #FRI-265 and O'Brien K, et al. ASBMR 2021, Abstract #1037; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

ENPP1-DEFICIENT PATIENTS PRESENT WITH BOTH SKELETAL COMPLICATIONS AND ECTOPIC CALCIFICATION

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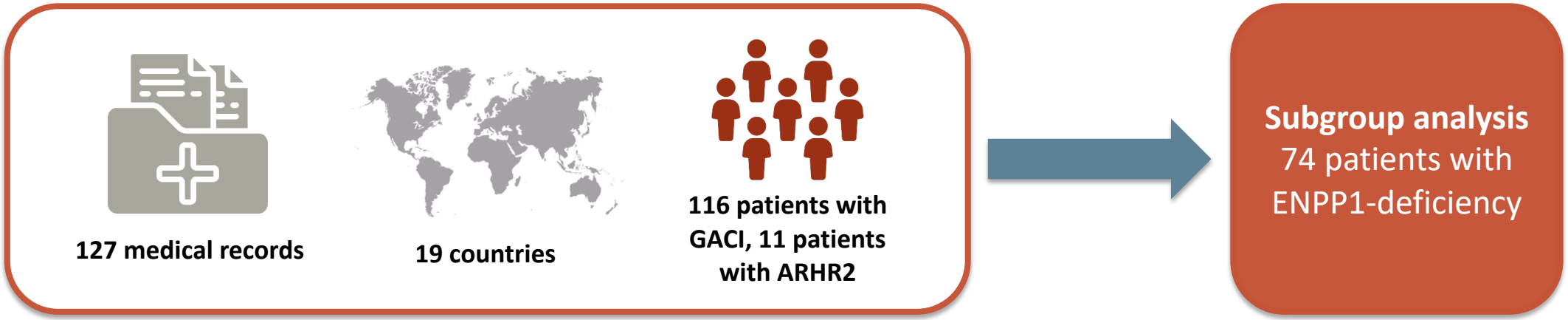
STUDY DESIGN

- Here we report a cross-sectional, **retrospective study of patients with ENPP1-deficiency**, characterising the prevalence and onset of skeletal complications to accelerate diagnosis and management



ARHR2, autosomal recessive hypophosphataemic rickets type 2; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; GACI, generalised arterial calcification of infancy

Rutsch F, et al. ASBMR 2021, Abstract #FRI-265; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

ENPP1-DEFICIENT PATIENTS PRESENT WITH BOTH SKELETAL COMPLICATIONS AND ECTOPIC CALCIFICATION

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KEY FINDINGS

- 46% presented with findings suggestive of rickets or osteomalacia (ie. altered gait, bowed extremities, metaphyseal cupping or short stature)
  - 25% of patients with skeletal complications did not have a diagnosis of GACI
- Rickets may be the first presentation for these patients and a diagnosis of ENPP1-deficiency should still be considered even if no prior history of calcification or GACI
- Currently the treatment of choice in the patients is an enzyme replacement therapy which prevents calcification of the vessels and may partially restore the skeletal phenotype but this has to be given twice a week
- Gene therapy being explored as a therapeutic option
- ENPP1 Deficiency should be considered as differential diagnosis in cases of rickets-like symptoms without alterations of vitamin D or phosphate levels

ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; GACI, generalised arterial calcification of infancy
Rutsch F, et al. ASBMR 2021, Abstract #FRI-265; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

TREATMENT WITH AN AAV VECTOR EXPRESSING ENPP1-FC PREVENTS ECTOPIC TISSUE CALCIFICATION AND RESTORES BONE PARAMETERS IN ENPP1 DEFICIENT MICE

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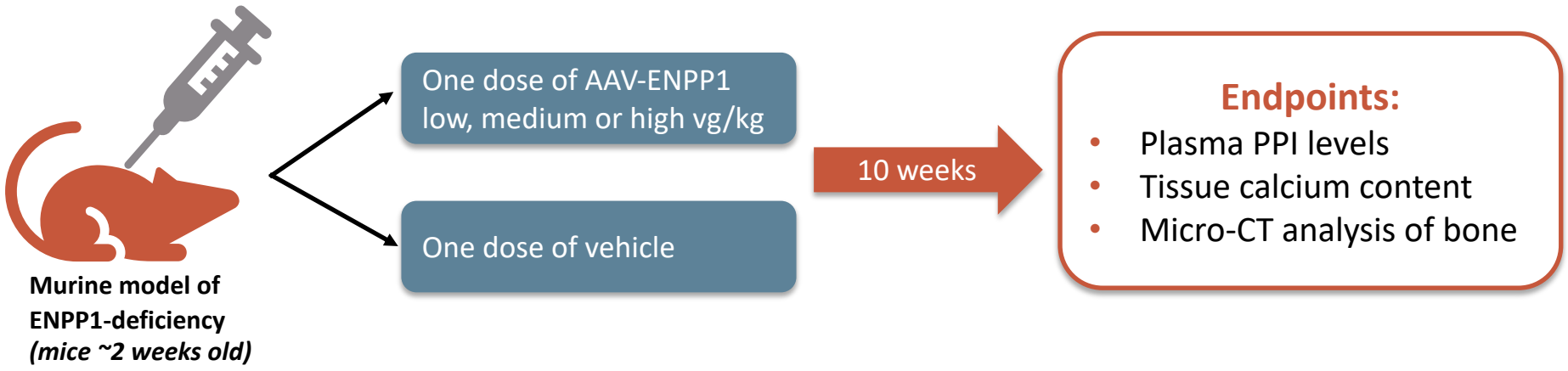
STUDY DESIGN

- An adeno-virus vector was developed expressing a modified human ENPP1-Fc as a potential treatment for ENPP1-deficiency, AAV-ENPP1
- The aim of this research was to develop a one-dose gene therapy to treat ENPP1-deficiency



AAV, adeno-virus vector; CT, computed tomography; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; PPI, inorganic pyrophosphate; vg, vector genomes
O'Brien K, et al. ASBMR 2021, Abstract #1037; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

TREATMENT WITH AN AAV VECTOR EXPRESSING ENPP1-FC PREVENTS ECTOPIC TISSUE CALCIFICATION AND RESTORES BONE PARAMETERS IN ENPP1 DEFICIENT MICE

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KEY FINDINGS

- Positive response to correct ENPP1-deficiency with this viral treatment
- After administration of a single dose of AAV-ENPP1 there was:
  - An increase in PPI levels
  - Decreased tissue calcification and improved mineralisation of the bones
  - An improved rickets-like phenotype
- Next steps would be to determine the lowest effective dose and conduct a safety assessment followed by clinical trials

ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; PPI, inorganic pyrophosphate
O'Brien K, et al. ASBMR 2021, Abstract #1037; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

ENPP1: CLINICAL PERSPECTIVES

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FROM: DR. SEMLER

- Normally a rickets-like X-ray is only conducted due to bowing of long bones or in cases of impaired bone mineralisation defects (vitamin D deficiency or phosphate wasting).
- X-rays of metaphyseal areas need to be taken also in cases of ectopic calcification
- Data presented at ASBMR show that ENPP1 has to be considered as a differential diagnosis for a rickets-like X-ray to distinguish between ENPP1-deficiency rickets and other hypophosphataemic rickets
- Genetic testing for *ENPP1*-deficiency should therefore be used as a routine part of clinical practice in the future in the workup of unclear rickets.

ENPP1, Ectonucleotide pyrophosphatase/phosphodiesterase 1
https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)

FOP: BACKGROUND

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- **Fibrodysplasia ossificans progressiva** (FOP) is **a rare and disabling autosomal dominant disease** involving extraskeletal bone formation
- **Characterised by congenital deformity of the great toes** and progressive heterotopic ossification
- **Heterotopic ossifications occur after painful inflammatory flare-ups** that can arise spontaneously or can be triggered by minor trauma. Each flare-up ultimately causes restriction of related-joints, and along with the others eventually leads to immobility
- The **causative gene of FOP is *activin A receptor type 1* (*ACVR1*)**, a bone morphogenetic protein-signaling component, which normally acts to inhibit osteoblastogenesis
- **Currently, there are no curative interventions**, and the mainstay of treatment is focused on symptomatic relief using brief courses of high-dose corticosteroids for flare-ups

ACVR1, activin A receptor type 1 ; FOP, fibrodysplasia ossificans progressiva

Kaplan F, et al. Bone 2020; 140:115539; Akyuz G, et al. Curr. Opin. Pediatr 2019;31:716-22; Pignolo R, et al. Front Endocrinol (Lausanne). 2020;10:908; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

PALOVAROTENE FOR THE TREATMENT OF FOP IN FEMALES AGED ≥8 AND MALES ≥10 YEARS: DATA FROM THE PHASE 3 MOVE TRIAL

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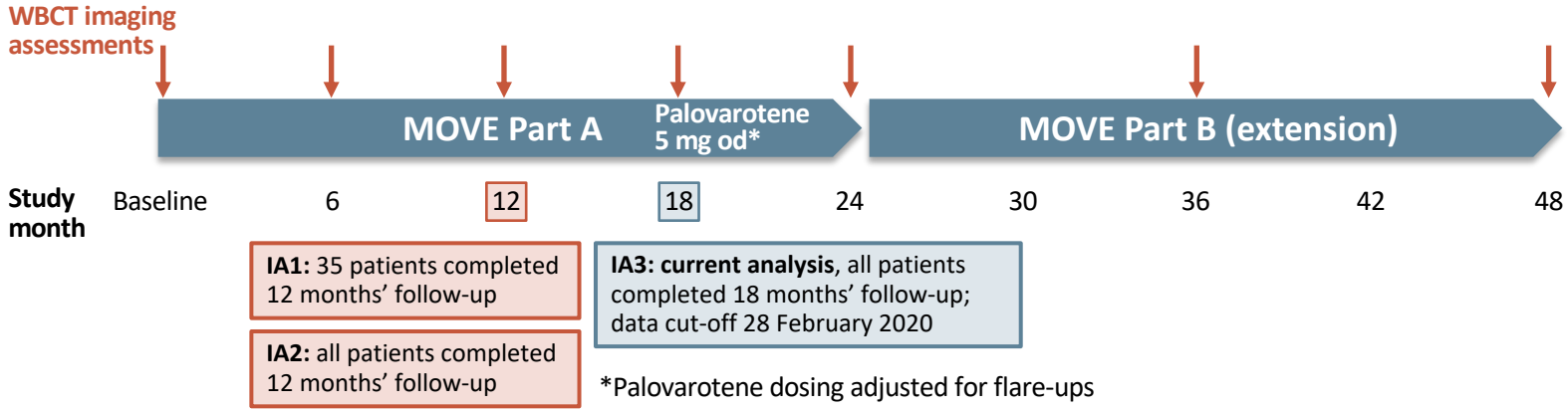
STUDY DESIGN

- Palovarotene is retinoic acid receptor gamma (RARγ) agonist
- MOVE trial (NCT03312634) – an efficacy and safety study of palovarotene for the treatment of FOP
  - Compared data from the MOVE trial with data from the Natural History Study (NHS; NCT02322255)
  - Data presented for females ≥8 years and males ≥10 years of age

Study population:
FOP pts ≥4 years of age with R206H ACVR1 mutation or other FOP associated with progressive HO



Endpoint:
Change in new HO volume assessed by low-dose WBCT

ACVR1, activin A receptor type 1; FOP, fibrodysplasia ossificans progressive; HO, heterotopic ossifications; IA, interim analysis; od, once daily; RARγ, retinoic acid receptor gamma; WBCT, whole body computed tomography

Pignolo R, et al. ASBMR 2021, Abstract #FRI-264; www.clinicaltrials.gov (NCT03312634); https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

PALOVAROTENE FOR THE TREATMENT OF FOP IN FEMALES AGED ≥8 AND MALES ≥10 YEARS: DATA FROM THE PHASE 3 MOVE TRIAL

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KEY FINDINGS

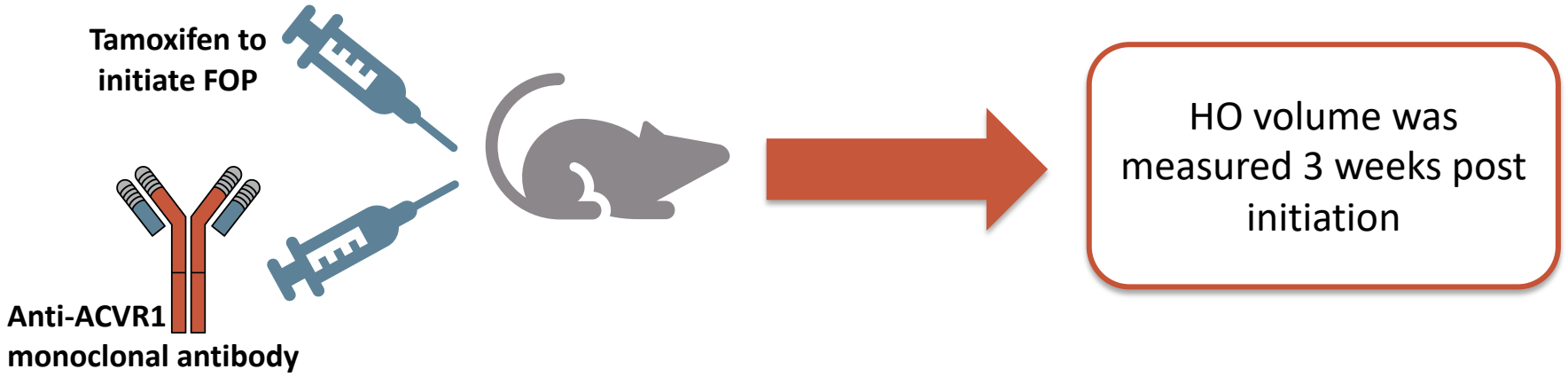
- 79 patients aged ≥8/10 years of age with a documented ACVR R206H mutation were enrolled in MOVE
- 88 subjects aged ≥8/10 years of age were treated in the NHS
- Mean annualised new HO volume was 57% lower in treated group after 18-month treatment period (consistent with the results from the overall MOVE population) versus the NHS
- The most common TEAEs were mucocutaneous events associated with retinoic acid
- Mucocutaneous treatment-emergent side effects were reported most commonly in the MOVE trial
- Premature physeal closure occurred in a number of patients (led to temporary hold of trial). Treatment is therefore limited until after closure of growth plates

ACVR, activin A receptor; FOP, fibrodysplasia ossificans progressive; HO, heterotopic ossifications; NHS, natural history study
Pignolo R, et al. ASBMR 2021, Abstract #FRI-264; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

ACVR1 ANTIBODIES EXACERBATE HETEROTOPIC OSSIFICATION IN FOP

STUDY DESIGN

- Previous results showed that HO in FOP is dependent on activation of FOP-mutant ACVR1 by a ligand, activin A
- The dependence on induction by activin A ligand suggested that inhibition of ligand-ACVR1 interaction using ACVR1 antibodies should have the same effect as inhibition of activin A
- It was hypothesised that a human antibody to activin A may be a potential therapeutic approach for FOP



ACVR1, activin A receptor type 1; CT, computed tomography; FOP, fibrodysplasia ossificans progressive; HO, heterotopic ossifications

Hatsell S, et al. Sci Transl Med. 2015;7(303):303ra137; Wang L, et al. ASBMR 2021, Abstract #1038; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

ACVR1 ANTIBODIES EXACERBATE HETEROTOPIC OSSIFICATION IN FOP

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KEY FINDINGS

- **Increase** of HO in the FOP mouse model
  - ACVR1 antibodies exacerbated HO in FOP
  - Therefore ACVR1 antibodies are definitely **not** a therapeutic option for FOP patients

ACVR1, activin A receptor type 1; FOP, fibrodysplasia ossificans progressive; HO, heterotopic ossifications
Wang L, et al. ASBMR 2021, Abstract #1038; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

THE MICROBIOME CONTRIBUTES TO ENDOCHONDRAL HETEROTYPIC OSSIFICATION IN FOP MICE BY REGULATING INNATE IMMUNE CELL RECRUITMENT AND POLARISATION

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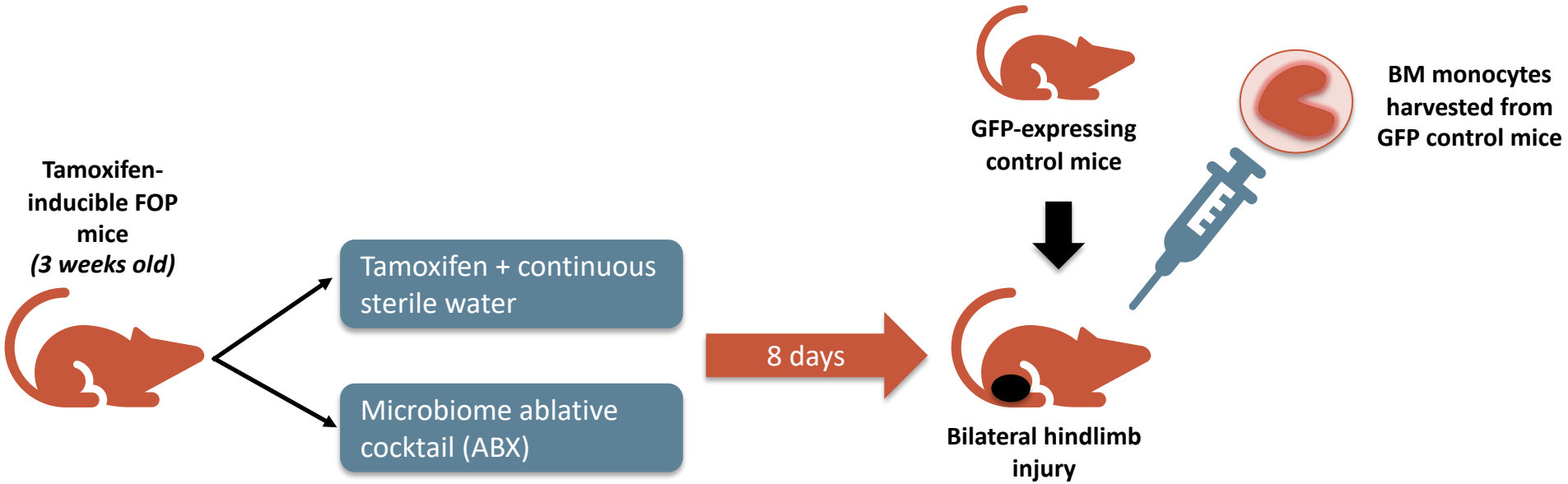
STUDY DESIGN

- Inflammation and innate immune cells contribute to FOP flares and HO
  - Inflammatory environmental factors could therefore contribute to disease variability in FOP patients
- Aim of this study was to reduce the HO formation by reducing the inflammatory activities in the mice and to determine whether ABX reduction in HO is mediated by changes in monocytes



ABX, ablative antibiotic cocktail; BM, bone marrow; FOP, fibrodysplasia ossificans progressive; GFP, green fluorescent protein; HO, heterotopic ossifications

Pierce J, et al. ASBMR 2021, Abstract #1039; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

THE MICROBIOME CONTRIBUTES TO ENDOCHONDRAL HETEROTYPIC OSSIFICATION IN FOP MICE BY REGULATING INNATE IMMUNE CELL RECRUITMENT AND POLARISATION

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KEY FINDINGS

- Microbiome-ablative ABX reduced HO in ABX-treated FOP mice
- Treatment decreased the expression of proinflammatory chemokines and receptors in injured FOP muscles
- Transplanting BM monocytes from control mice restored the HO phenotype in ABX-treated FOP mice
- Reducing the inflammatory process in FOP mice seems to have a beneficial therapeutic effect on HO formation

ABX, ablative antibiotic cocktail; BM, bone marrow; FOP, fibrodysplasia ossificans progressive; HO, heterotopic ossifications
Pierce J, et al. ASBMR 2021, Abstract #1039; https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

FOP: CLINICAL PERSPECTIVES

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FROM: DR. SEMLER

- A lot of activity and good ideas presented at ASBMR as to how to improve the care of FOP patients
- Some approaches have been shown to be more beneficial than others, e.g. palovarotene is one of the most developed and best approaches
- Other ways to influence the signalling pathway in the cell need to be further investigated. Initial results suggest regulating inflammation may be beneficial
- Very pleased that there is so much research ongoing in the rare bone disease area which is new
- Many studies in the pre-clinical stage that have promising data
- There is hope that a better treatment can be offered to these patients in the future

FOP, fibrodysplasia ossificans progressive
https://cor2ed.com/podcast-rare-bone-disease-highlights-at-asbmr-2021/

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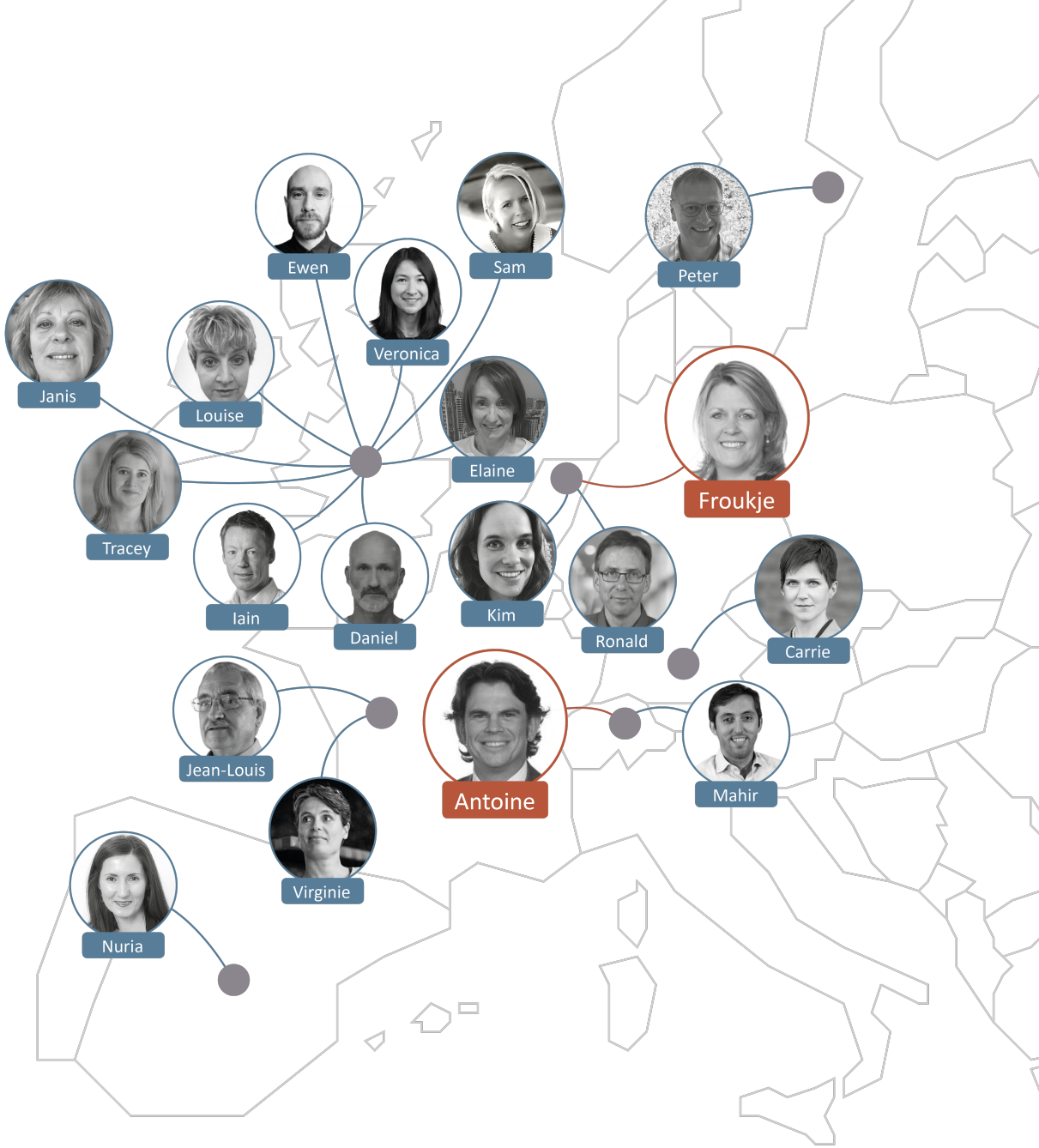

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