Marelise Eekhoff
(Amsterdam)

Richard Keen
(London)

Clemens Stockklausner
(Garmisch, Germany)

STOPFOP

Saracatinib trial TO Prevent FOP "STOPFOP"

A Phase 2A Clinical Trial

Bernard Smilde Amsterdam UMC

imi innovative medicines initiative

efpia

Alex Bullock
(Oxford)

Paul Yu
(Boston)

Dong Liu
(AstraZeneca, US)

Programme

-Introduction, STOPFOP executive centers	Marelise Eekhoff, MD, PhD
-What is Saracatinib and how does it work?	Alex Bullock, PhD
-General overview of the STOPFOP trial	Bernard Smilde, MD
-STOPFOP in the UK	Richard Keen, MD, PhD
-Q&A	

Clinical sites for STOPFOP trial

In Europe:

-Amsterdam (The Netherlands)

-Garmisch Partenkirchen (Germany)

-London (United Kingdom)

About Amsterdam

Marelise Eekhoff, PI

Bernard Smilde

Internal Medicine Section Endocrinology,
Amsterdam University Medical Centers - VUmc
Amsterdam Bone Center, The Netherlands

Amsterdam FOP team

FOP.Amsterdam@vumc.nl

Amsterdam UMC

- University hospital in the Netherlands with dedicated FOP research team
- Multidisciplinary centre treatment with multiple medical specialities with vast experience with FOP patients
- Easily accessible by car, train (and plane)

(Airport Amsterdam Schiphol is only 5 minutes by train; hotel next to the hospital)

FOP team members

Amsterdam, always fun to visit

Rijksmuseum

Zandvoort aan Zee

COVID-19 impact

Succesfully continued to provide care to all FOP trial patients during COVID-19 crisis

Access to multiple treatment locations (hospital as well out-patient clinics) to create a safe enviroment

Strict hospital and government measures in place to control spreading

Our way of working

-Cooperation, and safety

-International referral center

- *Diagnosis and follow-up*
- *Imaging center :[18F] NaF PET/CT*
- *Genetic center*

-Trials in FOP: -STOPFOP is open

Amsterdam UMC
Universitair Medisch Centra

Eekhoff et al Raijmakers. [18F]NaF PET/CT scan as an early marker of heterotopic ossification in FOP, Bone 2018 Apr;109:143-146

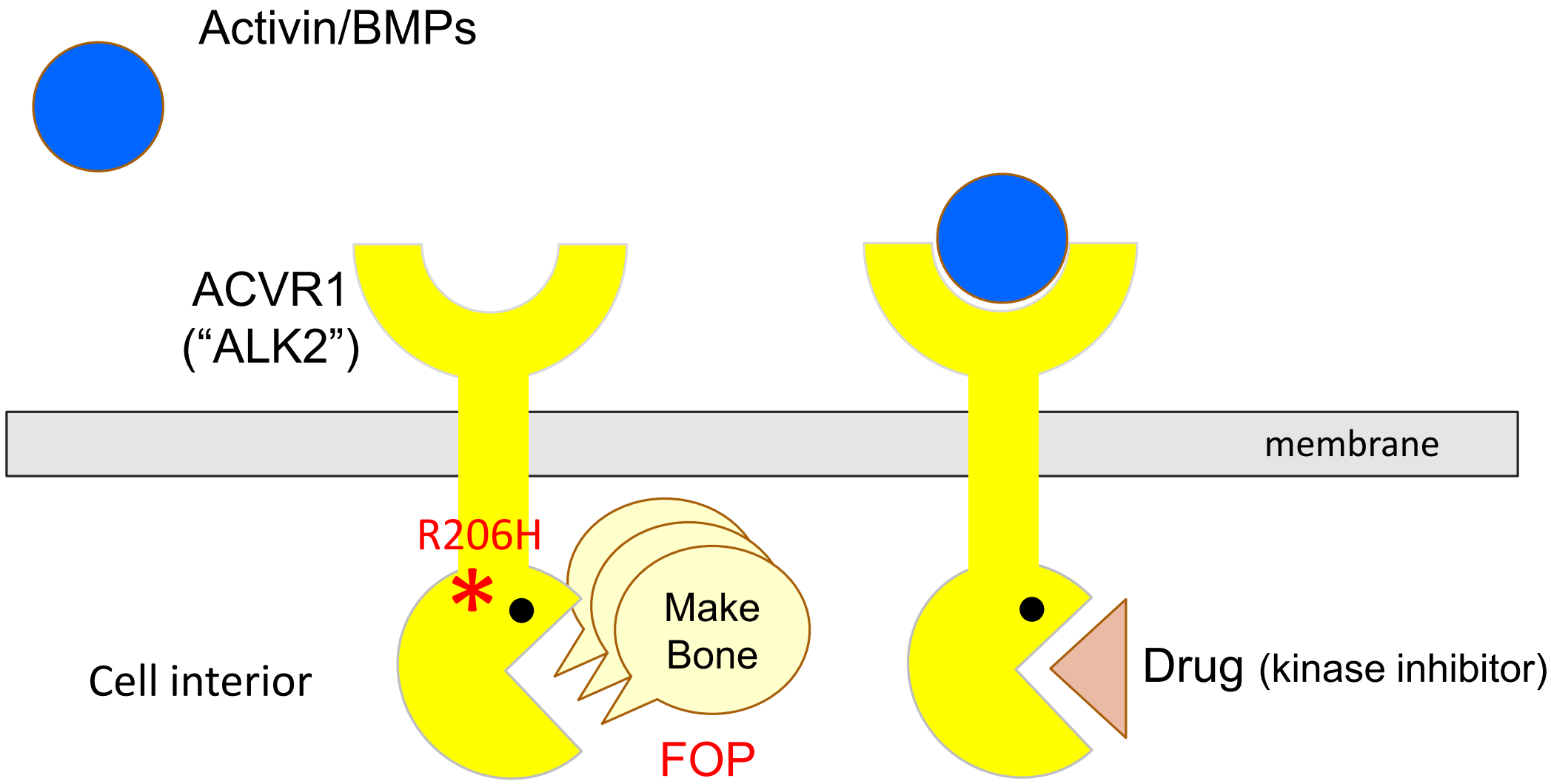
Botman E, et al, Eekhoff EMW.. Evolution of heterotopic bone in FOP. An [18F]NaF PET/CT study. Bone. 2019 Mar 8;124:1-6.

Alex Bullock

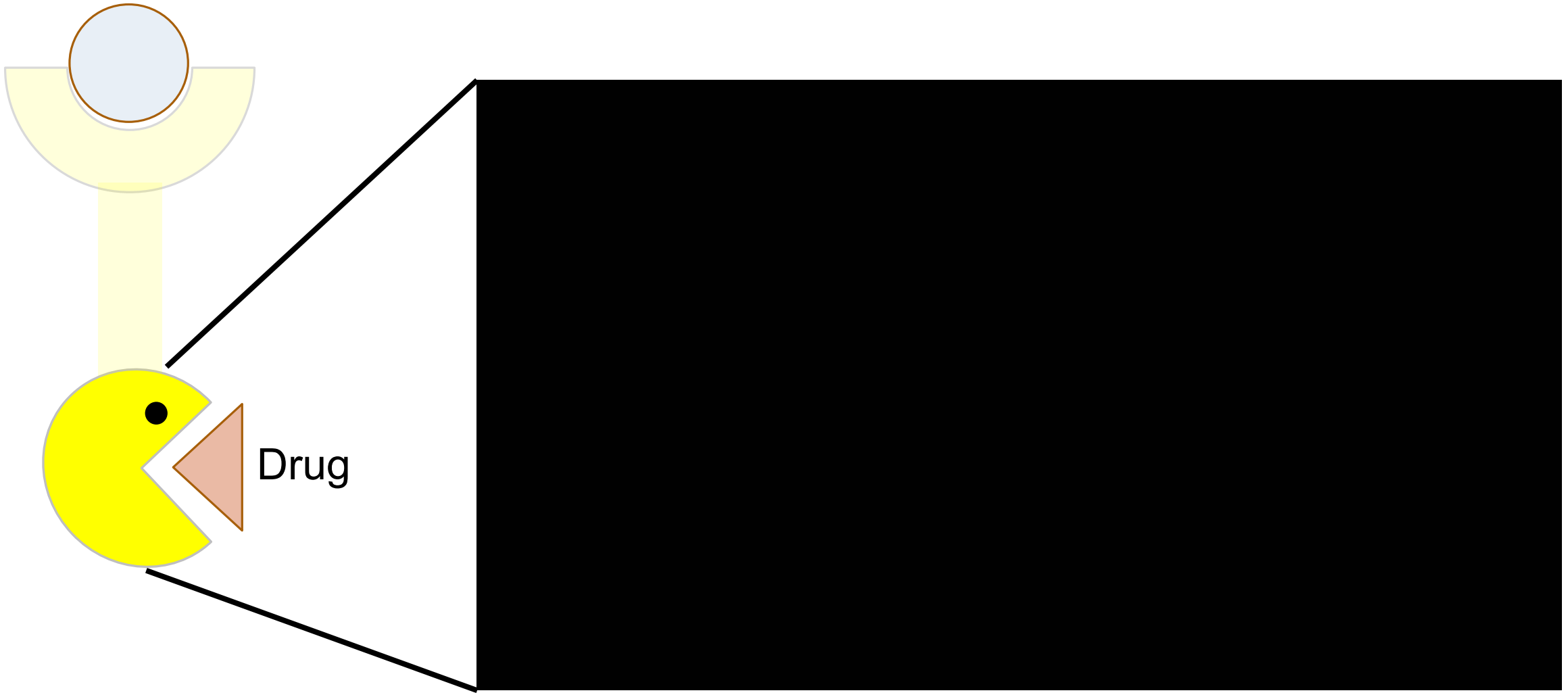
What is Saracatinib and how does it work?

University of Oxford

Our strategy to stop FOP

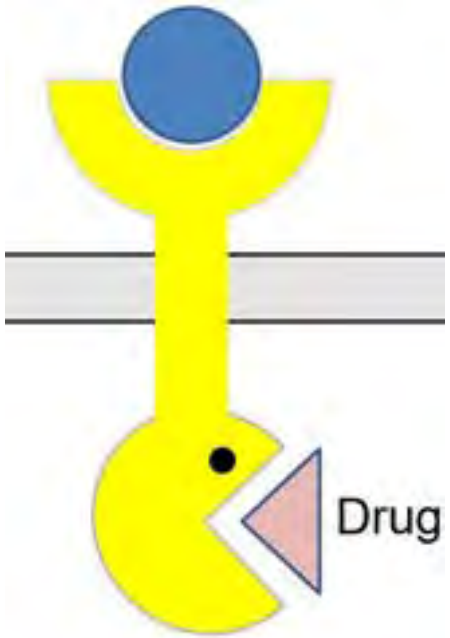


Movie showing how drugs can bind ACVR1

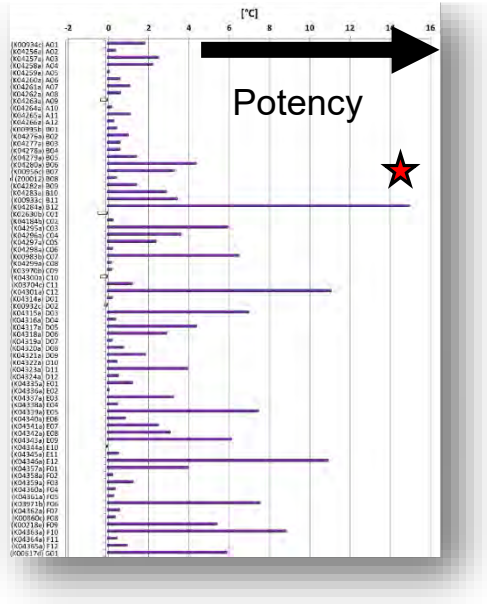


Drug discovery for ACVR1…does the shoe fit Cinderella?

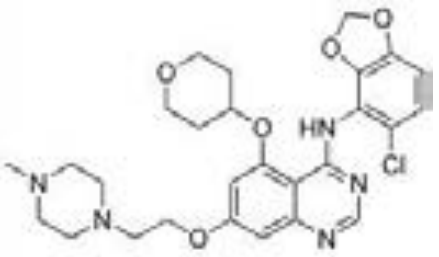
Searching for the best drug for the FOP protein



ACVR1
("ALK2")
receptor



Test each drug for
binding to FOP protein

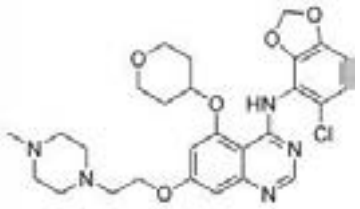


Saracatinib (AZD0530)

AstraZeneca
openinnovation

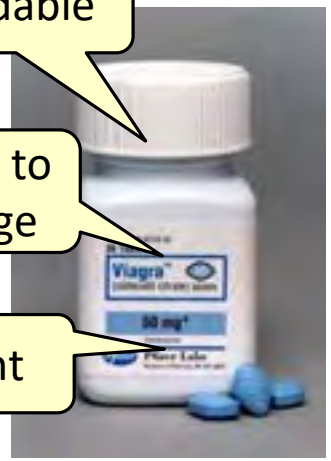
Ellie Williams, Oxford

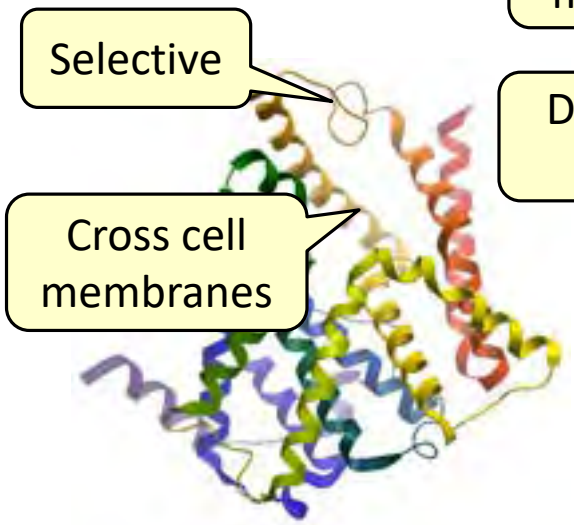
Many Factors to Drug Development Challenge

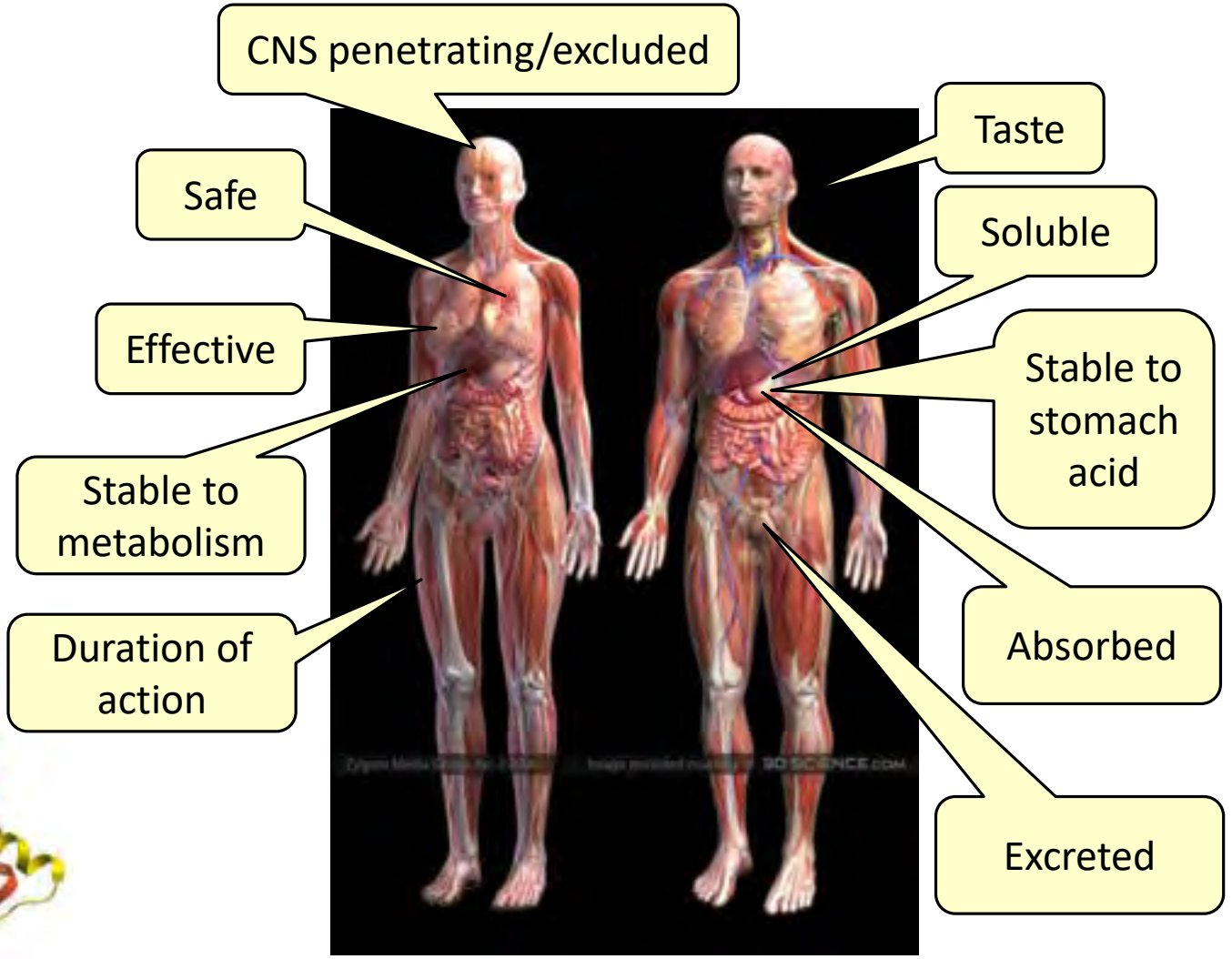


Saracatinib

AstraZeneca openinnovation





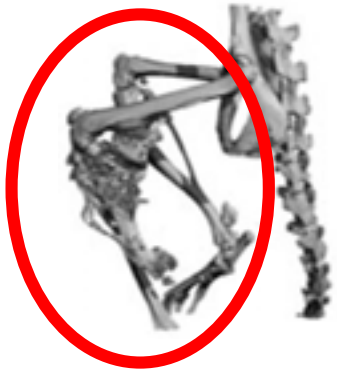


All of these things are determined by the chemical structure

Saracatinib stops FOP in the R206H mouse model

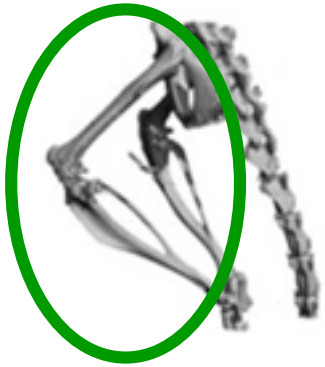
1. Disease Prevention *

No Drug



Unwanted bone

Treated with Saracatinib



FOP stopped

Dong-Dong Xia

Paul Yu (Harvard)

2. Using drug to allow surgery of FOP

Before surgery

Surgery (no drug)

6 weeks after surgery

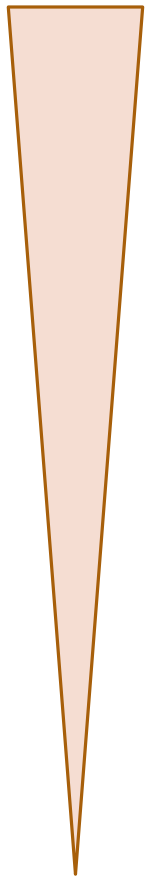
Unwanted bone regrows

Surgery (with Saracatinib)

Bone regrowth stopped

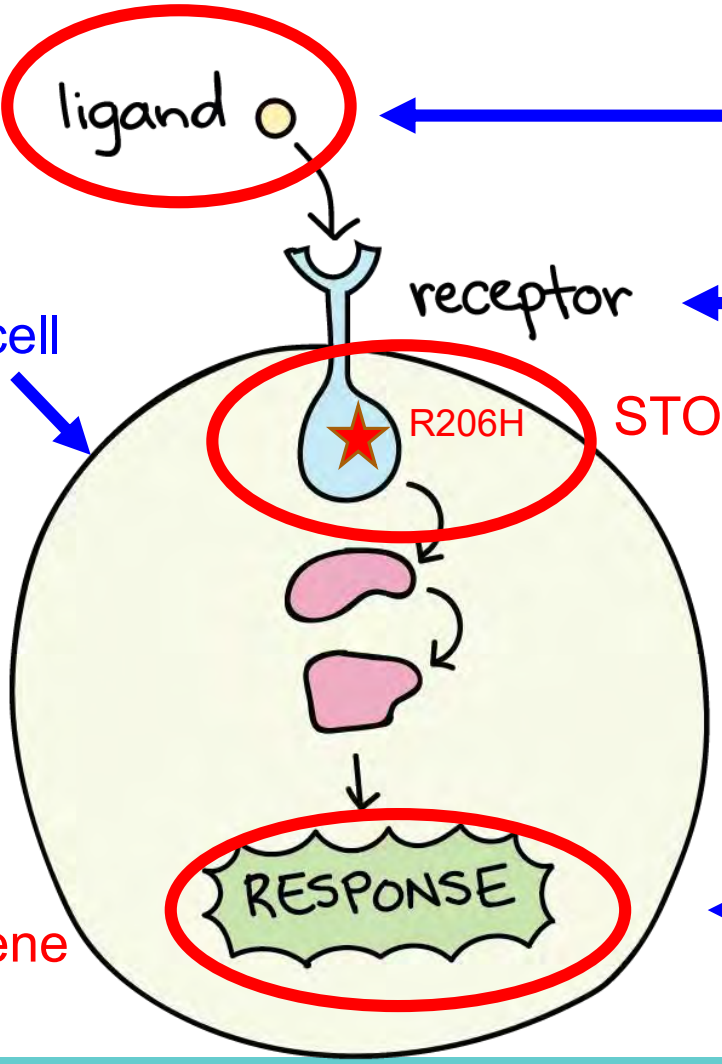
* Normal bone growth unaffected (bone length and bone density)

History of Saracatinib in clinical trials (>700 patients)



Dose (grams per day)	Disease	Clinical trial phase	Observations
1.000	**Healthy volunteers**	phase 1	Maximum tolerated single dose
0.175	**Cancer**	phase 2, 3	Treatment for 4-6 weeks with chemotherapy >600 patients
0.125	**Alzhiemer's disease** **LAM lung disease**	phase 2	Treatment for 9-12 months >100 patients (100-125 mg dose)
0.100	**STOPFOP**	phase 2	New clinical trial

Different drugs target different steps in FOP biology



Regeneron REGN2477 antibody

Hormone or Growth factor e.g. BMP or Activin

Human cell

The FOP protein (ALK2/ACVR1)

STOPFOP (saracatinib)

Chemical messengers relay the signal

Phosphate molecules added onto DNA-binding "SMAD" proteins

Clementia palovarotene

New genes turned ON or OFF
Stem cells may be told to grow as bone

Grant awarded for STOPFOP phase 2A clinical trial in FOP

- €1 Million for 3 year clinical trial
- AstraZeneca supplying the drug (€1 Million)
- Clinical trial to be designed and run by the academic team

(EU offices, Brussels) Left to right:
Dr Richard Keen (FOP clinician, London UK)
Dr David Hayes (AstraZeneca, USA)
Dr Marelise Eekhoff (FOP clinician, Amsterdam)
Dr Clemens Stockklausner (FOP clinician, Germany)
Dr Alex Bullock (FOP researcher, Oxford UK)

Drinks in Brussels after our grant “interview”

Left to right:
Prof Jim Triffitt (retired researcher, Oxford UK)
Dr Richard Keen (FOP clinician, London UK)

Left to right:
Dr Marelise Eekhoff (FOP clinician, Amsterdam)
Dr Clemens Stockklausner (FOP clinician, Germany)

STOPFOP general overview

BERNARD SMILDE, MD

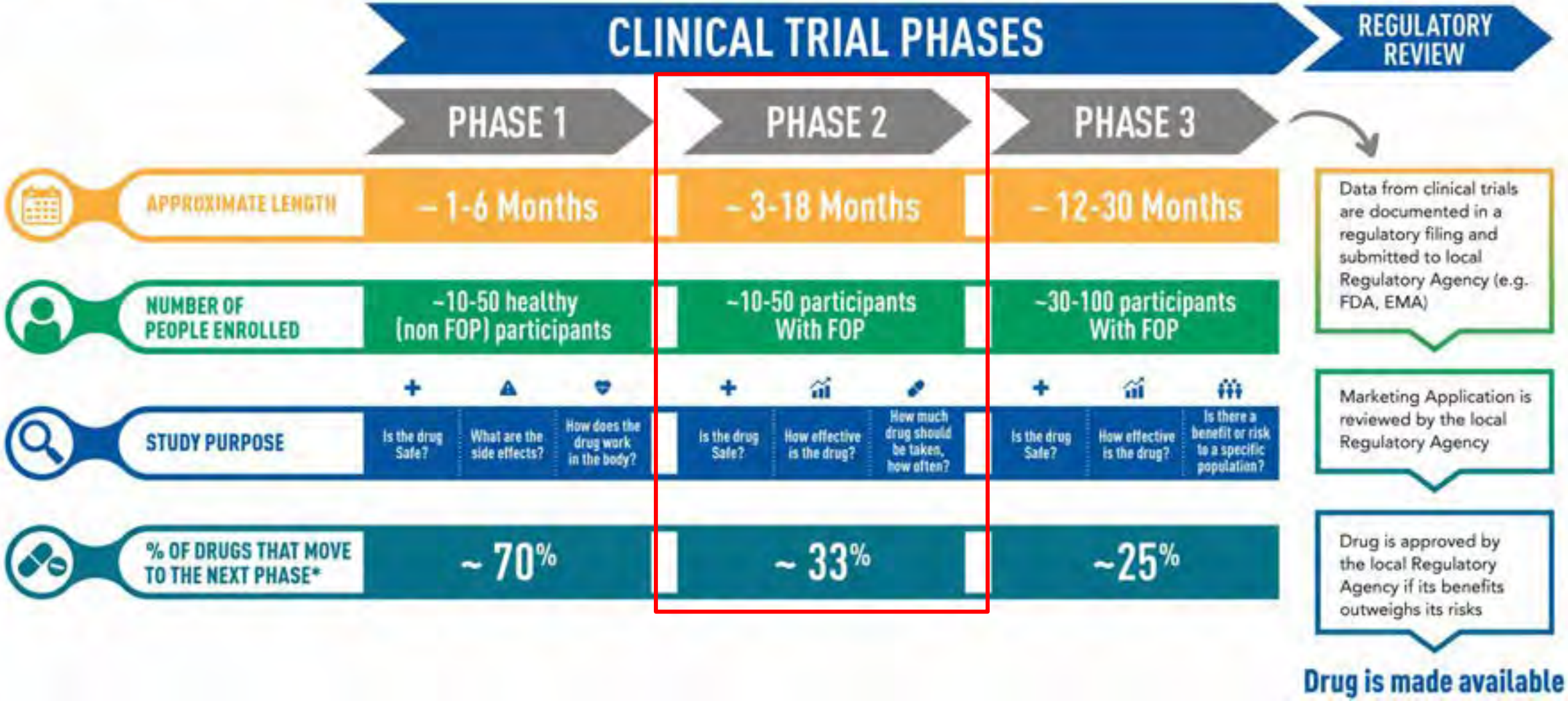
STOPFOP

- Saracatinib Trial TO Prevent FOP

- Investigator initiated
  - Sponsored by EU: Innovative Medicines Initative

- Partners
  - Consortium of several academic centers and AstraZeneca
  - Stakeholders board
    - IFOPA
    - National patients organisations of The Netherlands, United Kingdom, Germany, France, Italy and Sweden

HOW A DRUG MOVES THROUGH CLINICAL TRIALS
AND GETS TO PEOPLE WITH FOP



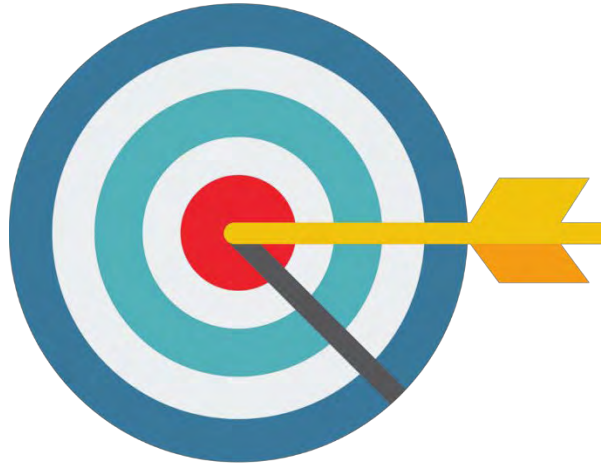
Aim

To investigate:

- The effectiveness of Saracatinib on FOP
  - PET-CT
  - Questionnaires/diary

- The safety of Saractinib in people with FOP
  - Side-effects
  - Blood results

<u>In order to discover an effective medicine to stop FOP</u>



Locations

3 clinical sites
- Netherlands (Amsterdam)
- Germany (Garmisch-Partenkirchen)
- United Kingdom (London)

Participation from patients outside of these countries is possible

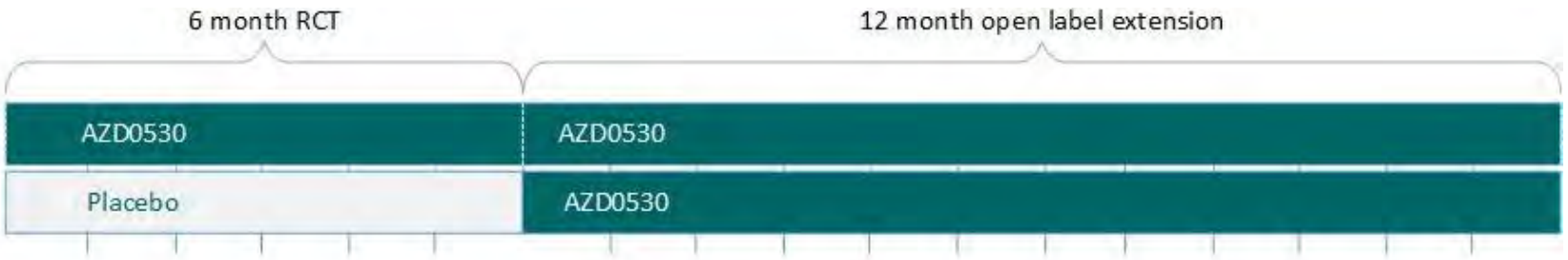
- European Union
- Case-by-case basis

Study Design

- 6 month Randomised controlled trial
  - 50% chance of treatment with Saracatinib
  - 50% chance of treatment with placebo (fake drug)

- 12 month open label extension phase
  - 100% chance of treatment with Saracatinib

- *Saracatinib can be continued after study period*



Study Design

-10 Visits in 18 months
- ~1 visit / 3 months
- Starts with eligibility visit

Daily oral administration of Saracatinib
- Medication can be crushed

- Diary
- Blood and urine collection
- Pulmonary and cardiac tests
- Questionnaires
- PET-CT

Who are we looking for?

- 20 FOP patients 18y-65y
  - Classic (R206H) mutation
  - Willing and able to participate (e.g. fit in CT-scanner)
  - Little other health issues

Contact

- www.STOPFOP.com
  - Contact form

- Email: b.smilde@amsterdamumc.nl

- Email UK: richard.keen1@nhs.net

STOPFOP Amsterdam team acknowledgements

Roel
Wouters
Ethicist

Gracielle
Schutjens
Monitor

Natasja van
Schoor
Statistician

EU helpdesk
team
Amsterdam
UMC VU

STOPFOP in the UK

Richard Keen

What will participation at RNOH involve?

Professor Richard Keen BSc PhD FRCP
Consultant in Metabolic Bone Disease
Royal National Orthopaedic Hospital, Stanmore

richard.keen1@nhs.net

The RNOH is an ideal location

Good access to motorway networks-M25/M1

Nearby airports-Heathrow, Luton, Stanstead

Local hotels

Free car parking on-site!

Stanmore-ideal for fun days out

WEMBLEY

Green Hospital-Covid negative

Team experienced in FOP clinical care and research

Down Town after the PET scan

Making life as easy and stress free as possible

Work alongside routine NHS appointments where possible

F2F reviews vs Virtual clinics - the “new normal”

Continuity of care-established clinical and research teams

Helping access additional funding/support

Questions?