

ACVR1/ALK2 kinase inhibitors for FOP and future directions

Inibitori della chinasi ACVR1/ALK2 per la FOP e prospettive future

Prof Alex Bullock

FOP Italia, Livorno, 2026

What does the FOP gene ACVR1 do?

Qual è la funzione del gene ACVR1 responsabile della FOP?

How does it cause FOP?

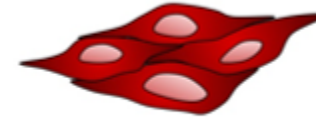
Come causa la FOP?

How are we designing drugs to stop it?

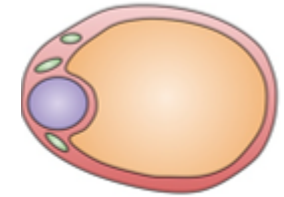
Come stiamo sviluppando farmaci per contrastarla?

You are made up of cells

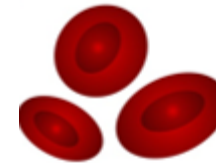
Sei composto da cellule



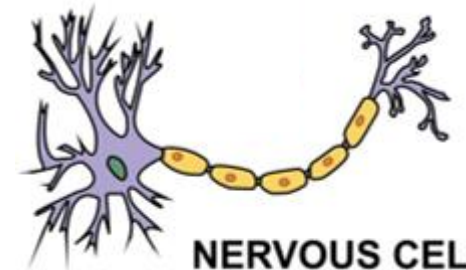
MUSCLE CELL
cellula muscolare



FAT CELL
cellula adiposa



BLOOD CELL
cellula del sangue



NERVOUS CELL
Nervo cella

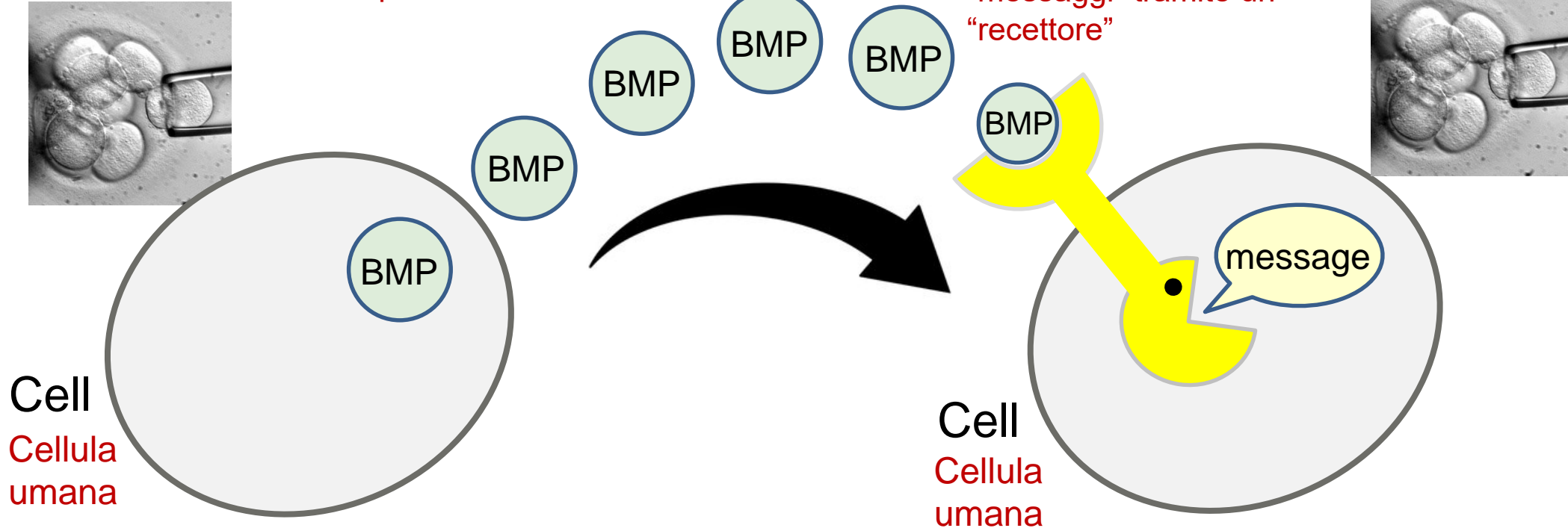
ETC

Your cells must “talk” to each other

Le tue cellule devono "comunicare" tra loro

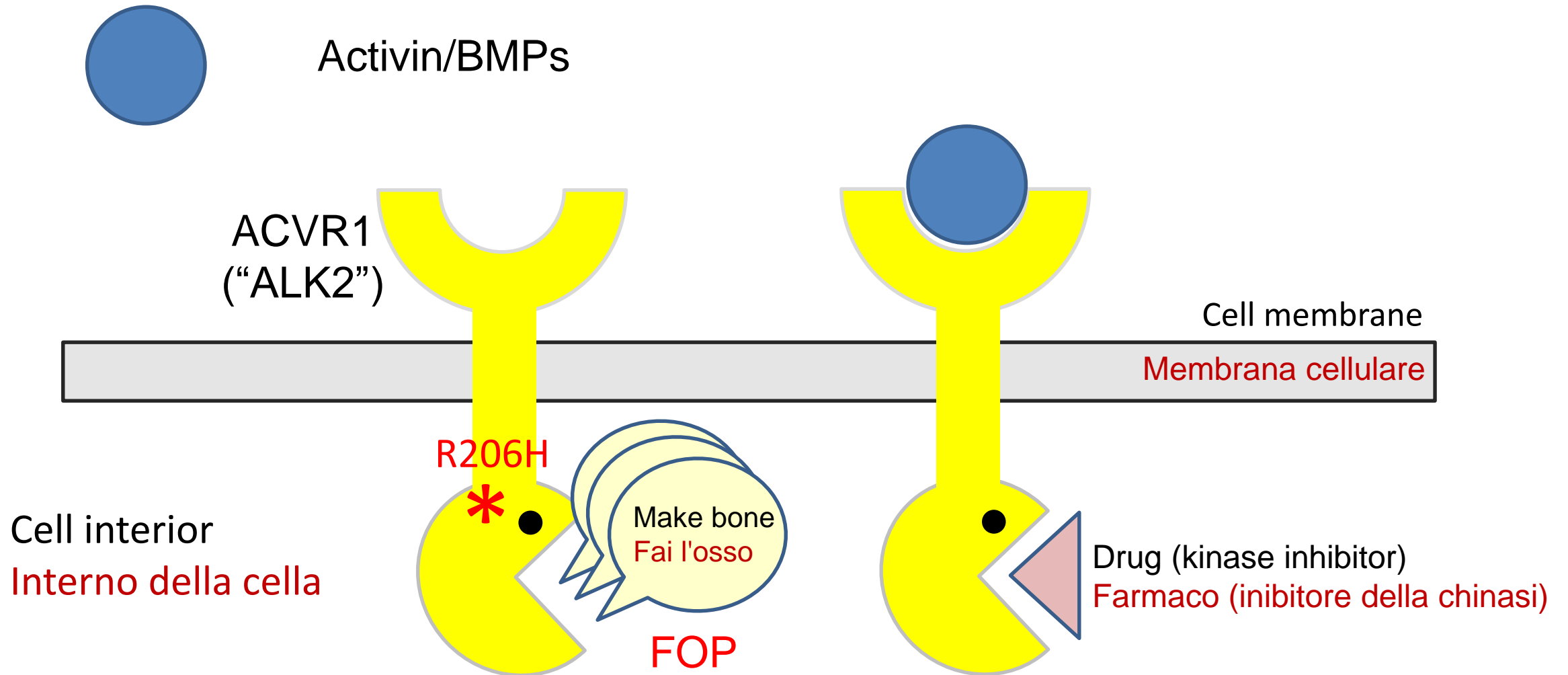
Cell sends “message” as
BMP or activin proteins
La cellula invia un
“messaggio” sotto forma di
proteine BMP o attivina

2nd Cell receives
“messages” via a “receptor”
La seconda cellula riceve i
“messaggi” tramite un
“recettore”



FOP gene ACVR1 codes for a receptor

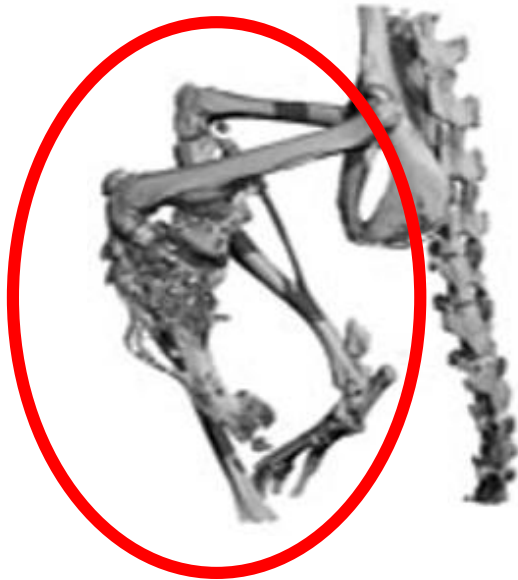
Il gene FOP ACVR1 codifica per un recettore



Saracatinib stops FOP bone lesions in mice

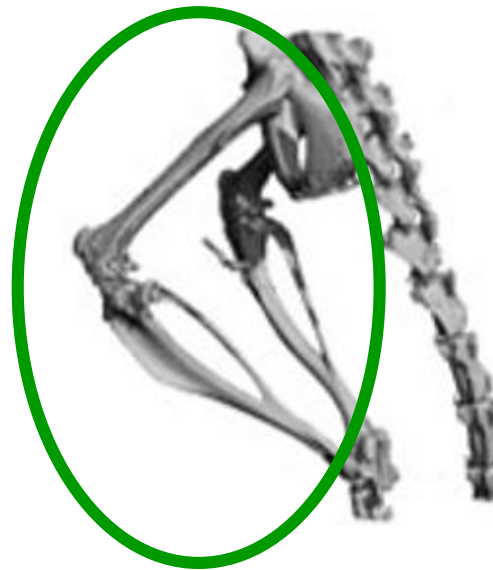
Il saracatinib arresta le lesioni ossee della FOP nei topi

No Drug
Nessuna medicina



Unwanted bone
Osso indesiderato

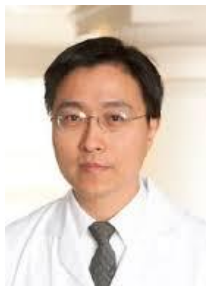
+ Saracatinib



FOP stopped
La FOP è stata interrotta



“STOPFOP”
clinical trial
sperimentazione
clinica



Paul Yu (Harvard)



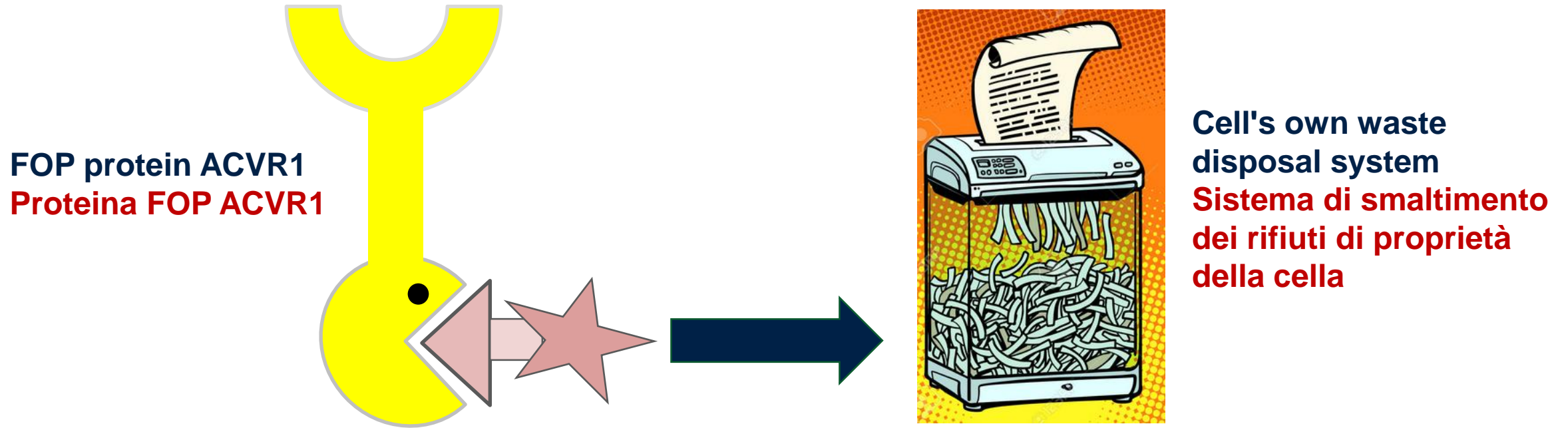
Marelise Eekhoff (Amsterdam)

For the future? Could we try to design even better drugs?
Per il futuro? Potremmo provare a creare farmaci ancora migliori?



We can design drugs to destroy the FOP protein ACVR1

Possiamo progettare farmaci per distruggere la proteina FOP ACVR1

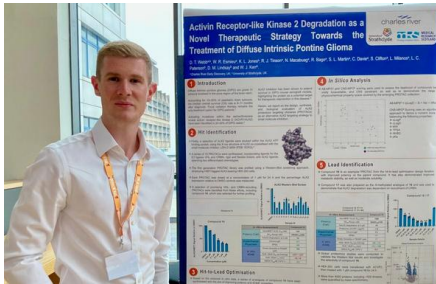


Bifunctional drug directs ACVR1 protein to the shredder
Un farmaco bifunzionale distrugge la proteina ACVR1

Team collaborations

Collaborazioni di squadra

PhD students
Studenti di dottorato



Daniel Webb



University of
Strathclyde
Glasgow

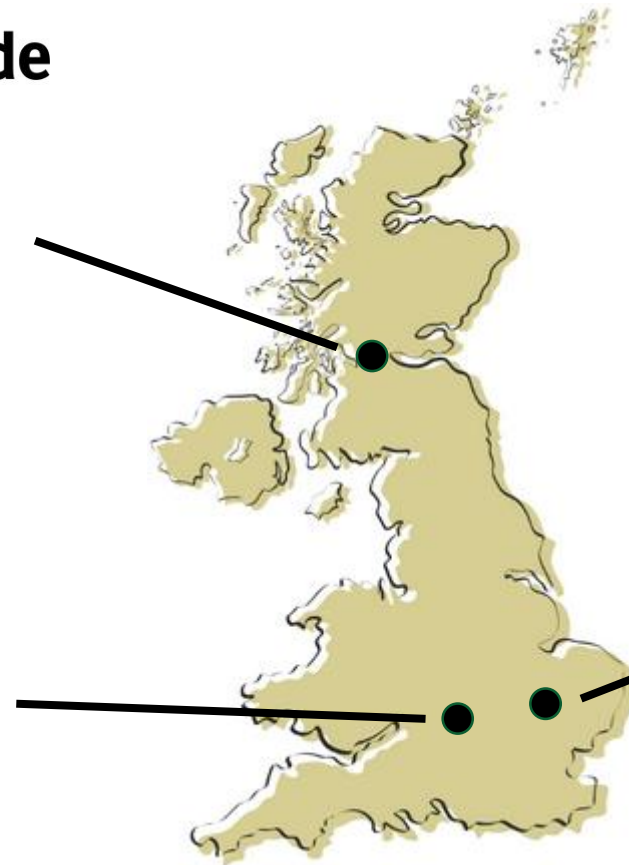
David M. Lindsay
William J. Kerr



Kyle Ferguson



Alex Bullock

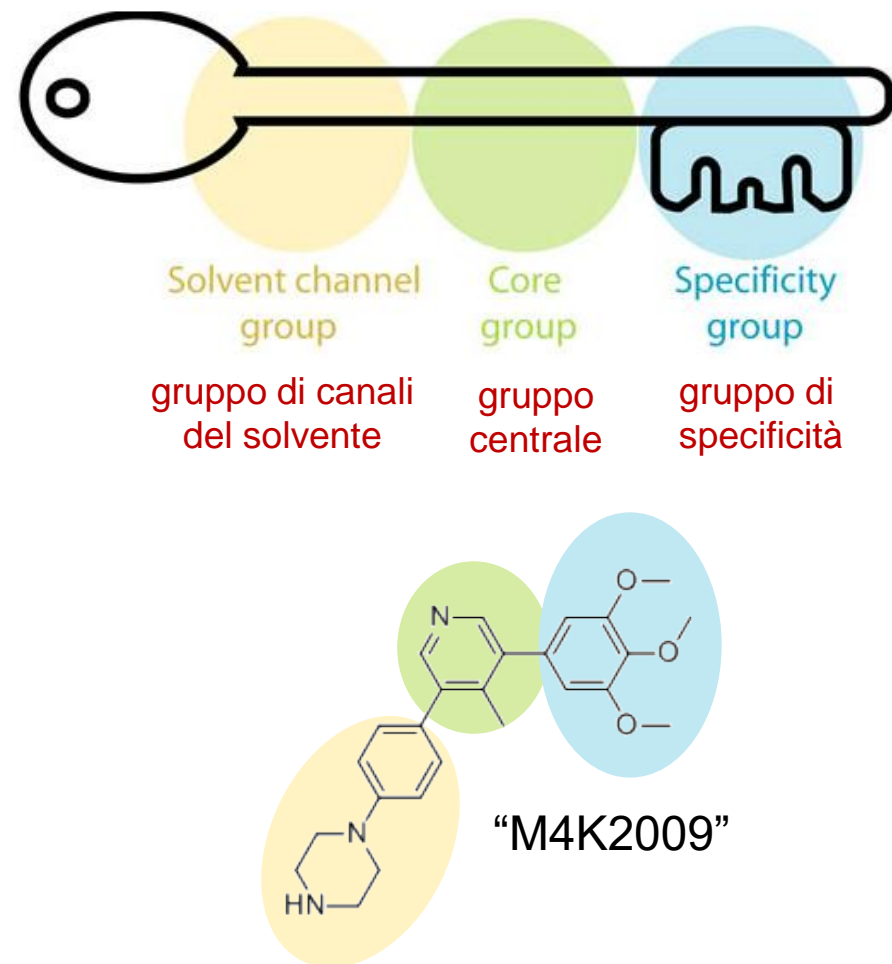
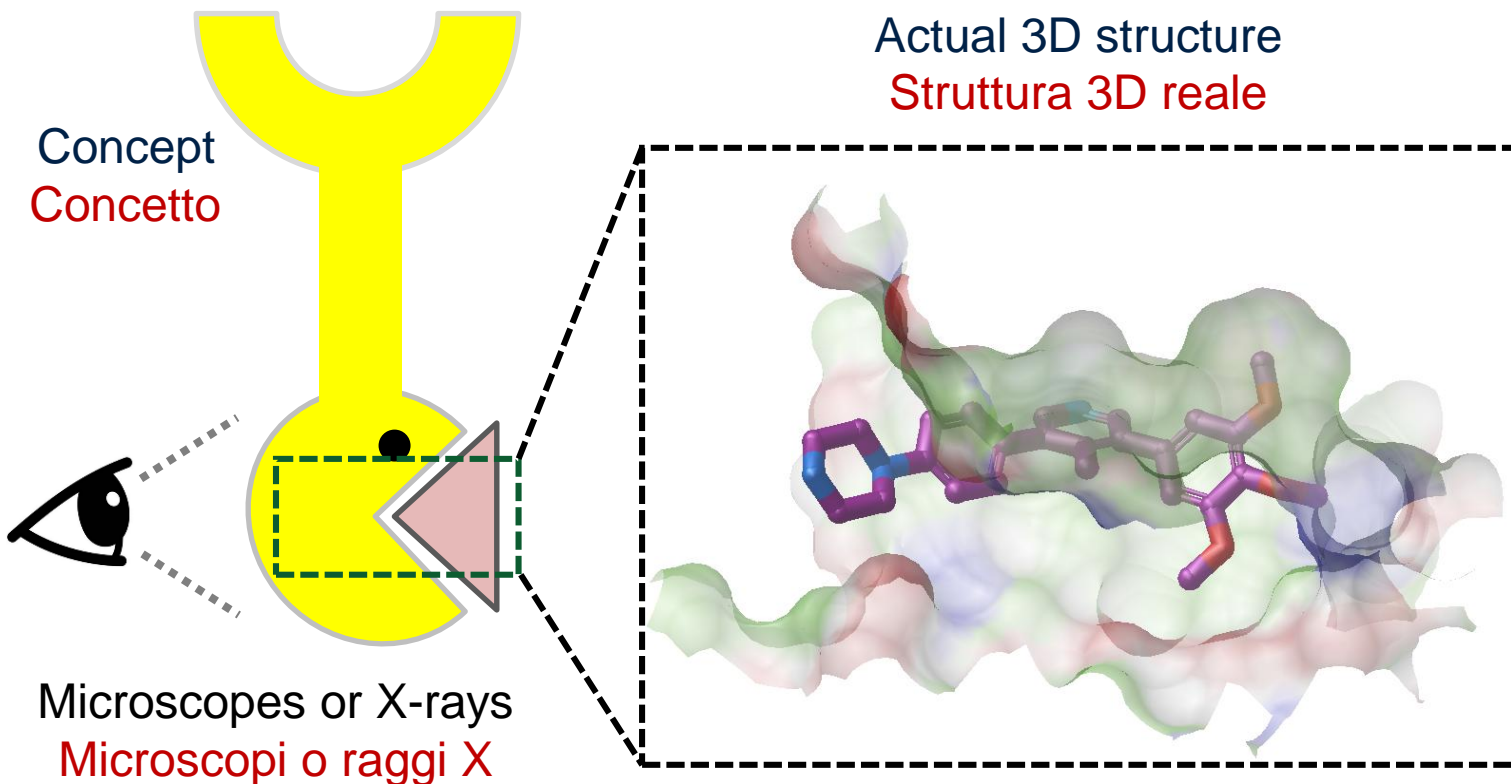


charles river

William R. Esmieu
Katherine L. Jones

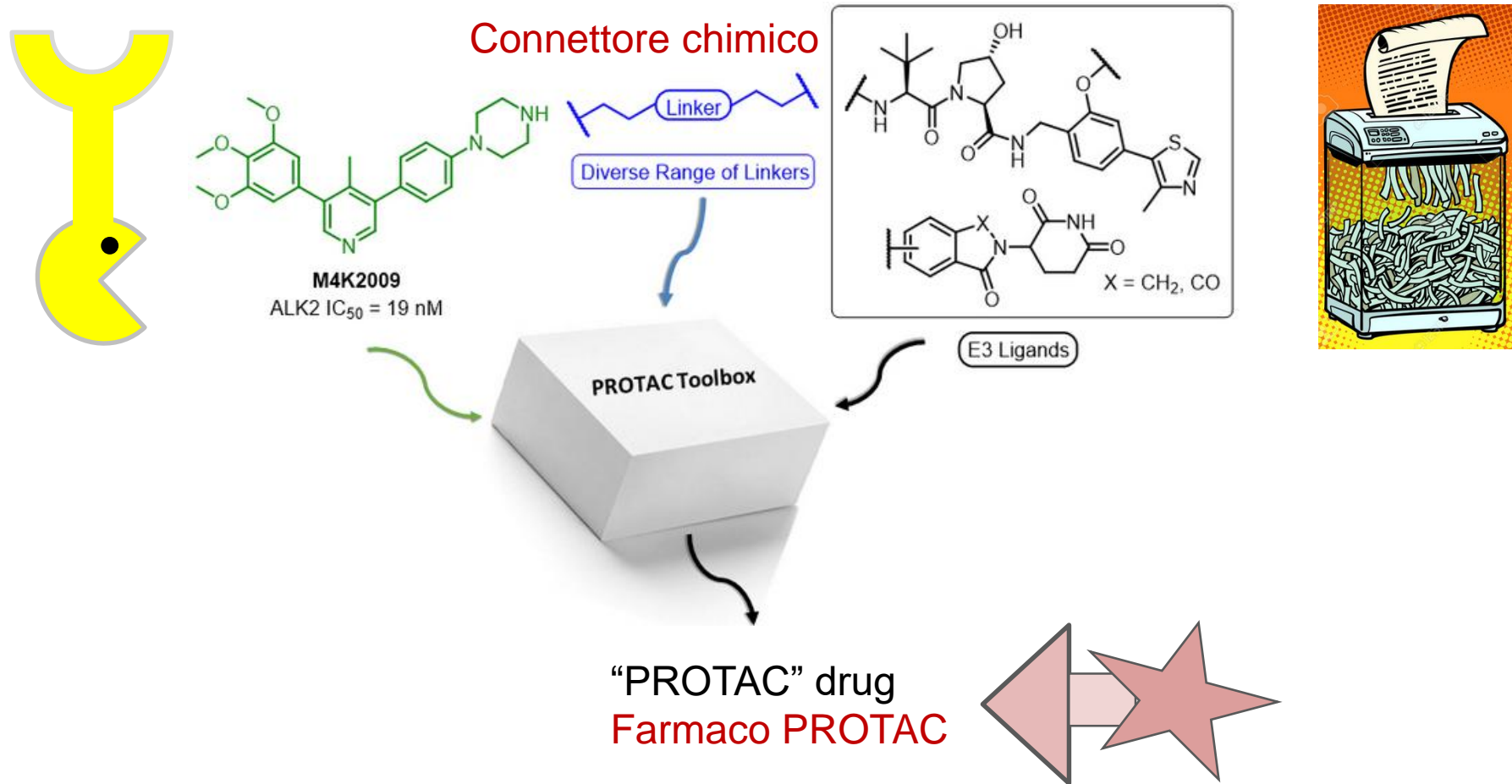
ACVR1 drug design – a lock and key analogy

Progettazione di farmaci: un'analogia tra chiave e serratura



Designing biofunctional drugs

Progettazione del nostro farmaco biofunzionale

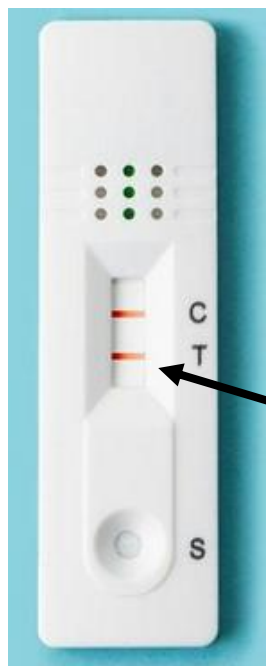


Daniel Webb
William R. Esmieu
David M. Lindsay
William J. Kerr

Testing if the drugs destroy the FOP protein ACVR1

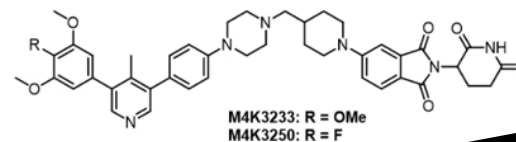
Verificare se i farmaci distruggono la proteina FOP ACVR1

COVID test **ProvaCOVID**

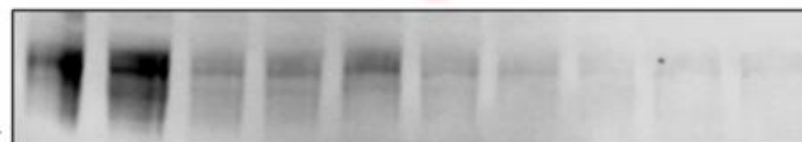


COVID protein detected
Rilevata proteina COVID

FOP protein test **Test per la proteina FOP**



Drug dose increased
La dose del farmaco è aumentata



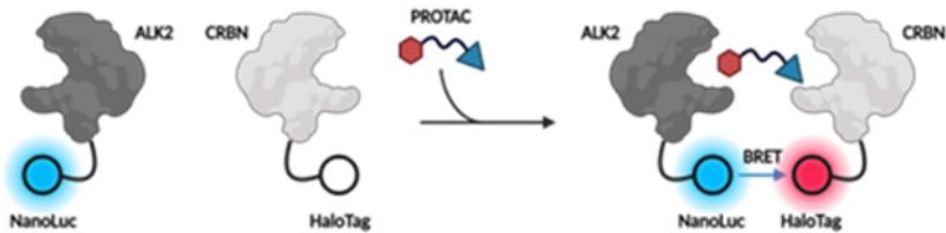
FOP protein detected
Rilevata proteina FOP



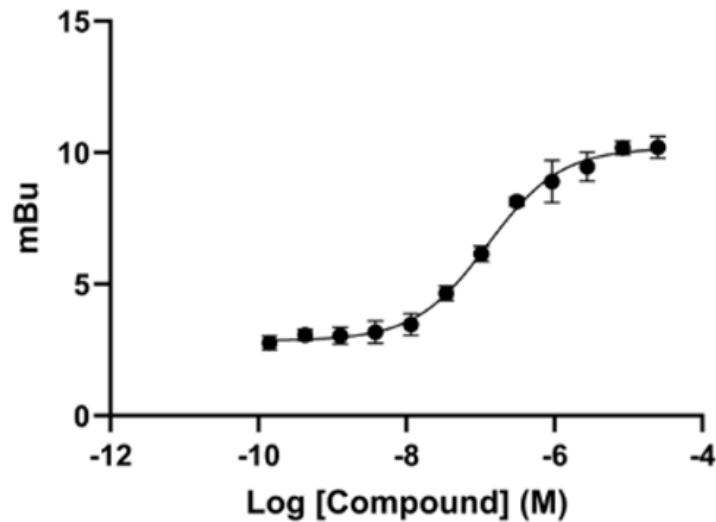
Testing drug potency and selectivity

Test di potenza e selettività dei farmaci

Drug potency *potenza del farmaco*

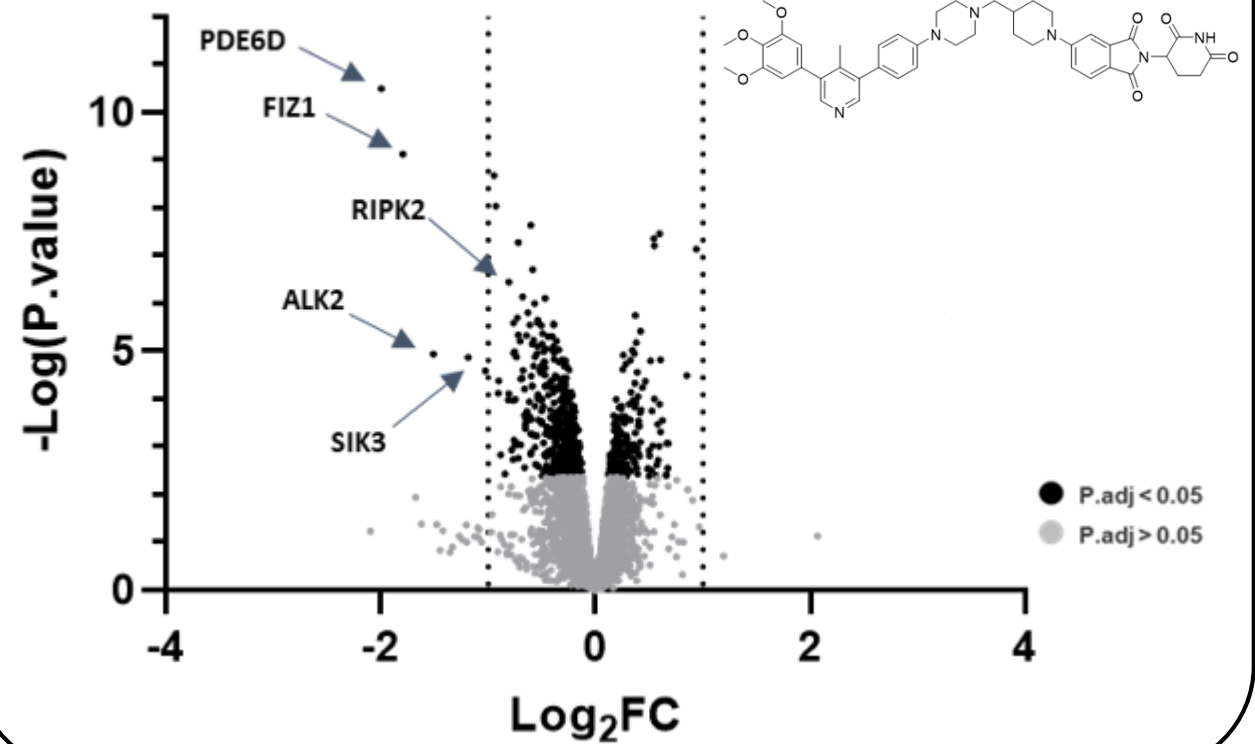


M4K3233 NanoBRET PPI



Drug selectivity *selettività dei farmaci*

M4K3233 HEK-293



Publication submitted / Pubblicazione in arrivo

Targeting Activin Receptor-like Kinase 2 Using Heterobifunctional Protein Degraders

Daniel T. Webb, Katherine L. Jones, Natsuko Macabuag, Ruzica Bago, Joshua Betts, Sumit Bhattacharyya, Steve Clifton, Ryan J. Tinson, Chigozie Achara, Simon Gilbert, Stefanie Howell, David H. Drewry, Rebecca Rogers, Chris Jones, Kyle R. Ferguson, Alex N. Bullock, David M. Lindsay, William J. Kerr and William R. Esmieu.

Conclusions / Conclusioni riassuntive

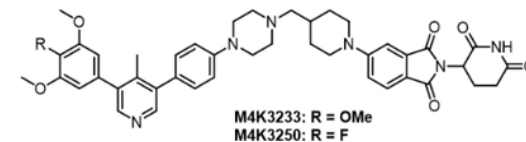
- Drugs could remove the FOP protein
I farmaci potrebbero rimuovere la proteina FOP
- This could potentially give stronger protection against FOP
Ciò potrebbe potenzialmente fornire una protezione più forte contro la FOP
- More chemistry and more testing would be needed
Sarebbero necessari più chimica e più test

Example M4K3250 drug properties

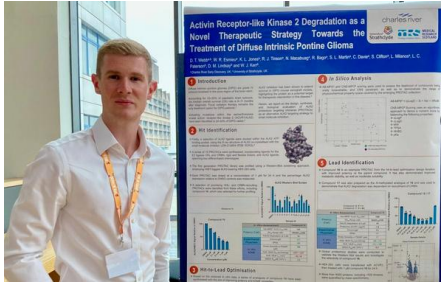
Drug concentration for 50% degradation, pDC₅₀ = 7.9

Maximum degradation, D_{Max} = 78%

Ternary ACVR1-Cereblon complex binding potency pEC₅₀ = 6.9 ± 0.27



Special acknowledgements / Ringraziamenti speciali



Daniel Webb



University of
Strathclyde
Glasgow

David M. Lindsay
William J. Kerr


charles river
William R. Esmieu & team

 **Massachusetts General Hospital**
Founding Member, Mass General Brigham

Paul Yu & team



Kyle Ferguson



Ellie Williams
Georgina Kerr



Marelise Eekhoff
Clemens Stockklausner
Vincent Verheij
Jing Cui
Paul Yu
Richard Keen



FOP families visiting the laboratory

Le famiglie della FOP visitano il laboratorio



University of Oxford laboratory

