3rd Annual Course

Pharmacogenetics and Personalised Medicine

The phosphatase, pp2a as a classifier to stratify patients into therapeutic groups

Dr Godfrey Grech
Pathology Department
University of Malta

Thursday 9th - Friday 10th February 2012
Aula Magna Sapienza University of Roma

3rd Annual Course

Pharmacogenetics and Personalised Medicine

Cellular models utilised to study mechanism of disease

Identification of potential therapeutic targets

Genomics used to stratify patients into subtypes

Biomarkers used as classifiers of specific therapeutic groups

3rd Annual Course

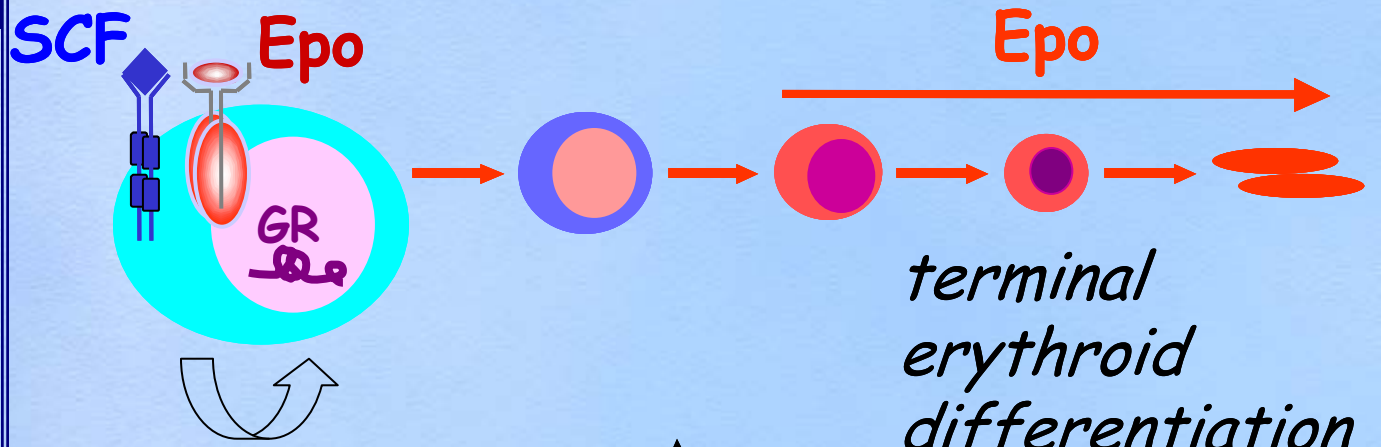
Pharmacogenetics and Personalised Medicine

Mechanism of Disease

Therapeutic targets

Biomarkers

Model system



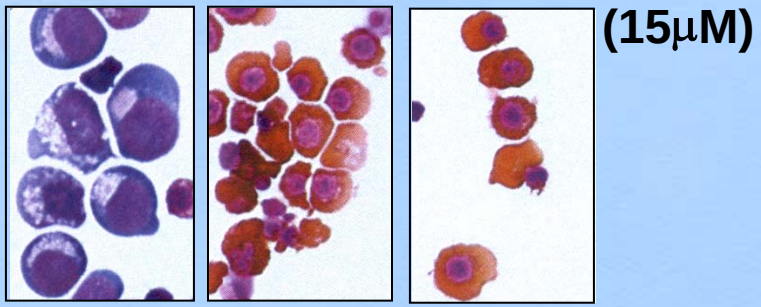
Renewal

Epo

SCF

glucocorticoids

LY294002



3rd Annual Course

Pharmacogenetics and Personalised Medicine

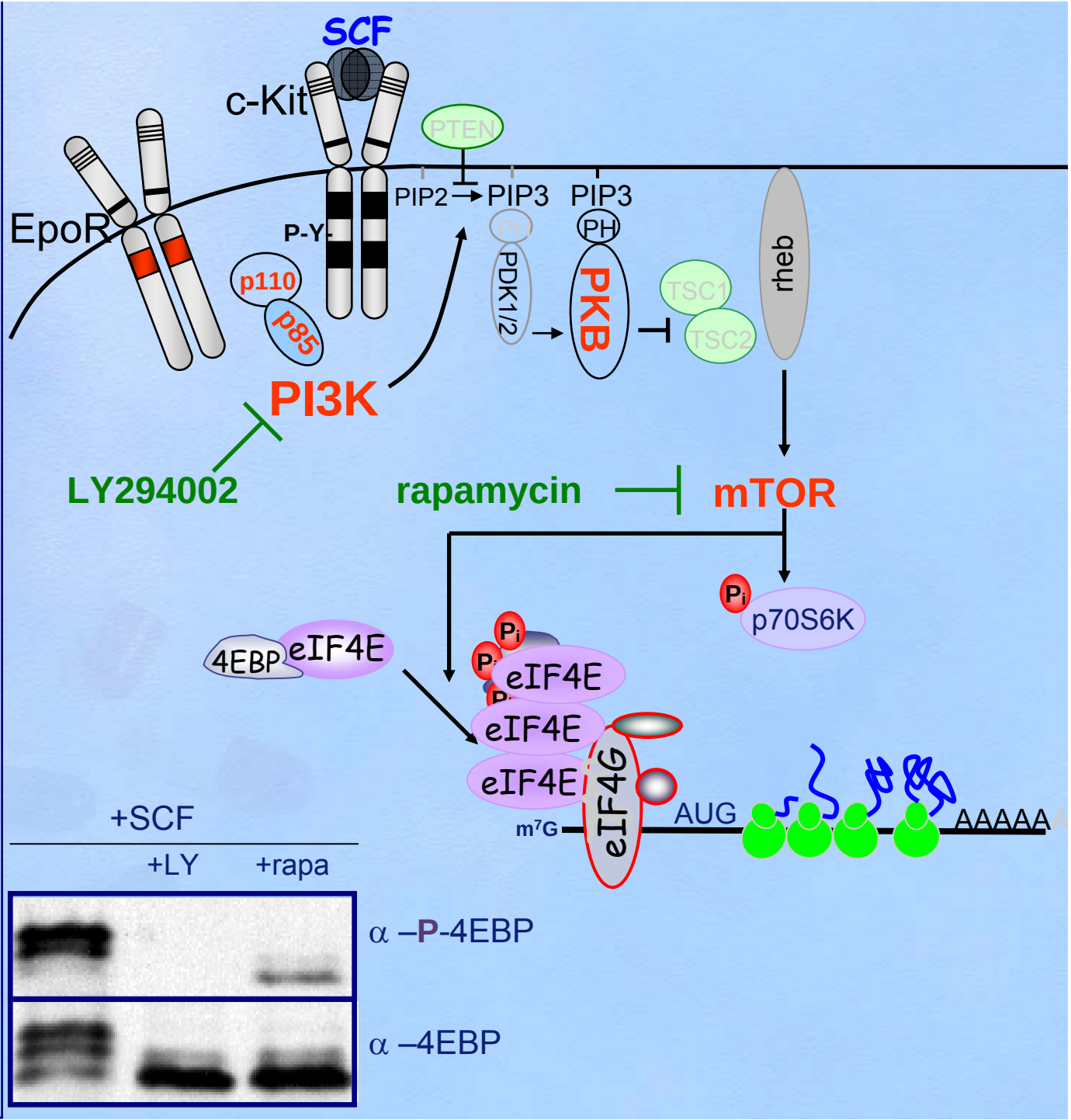
Mechanism of Disease

Therapeutic targets

Biomarkers

Blazquez-Domingo, M.*, **Grech, G.*** and von Lindern, M. (**2005**) Translation Initiation Factor 4E Inhibits Differentiation of Erythroid Progenitors.

Mol. Cell. Biol., 25, 8496-8506.



3rd Annual Course

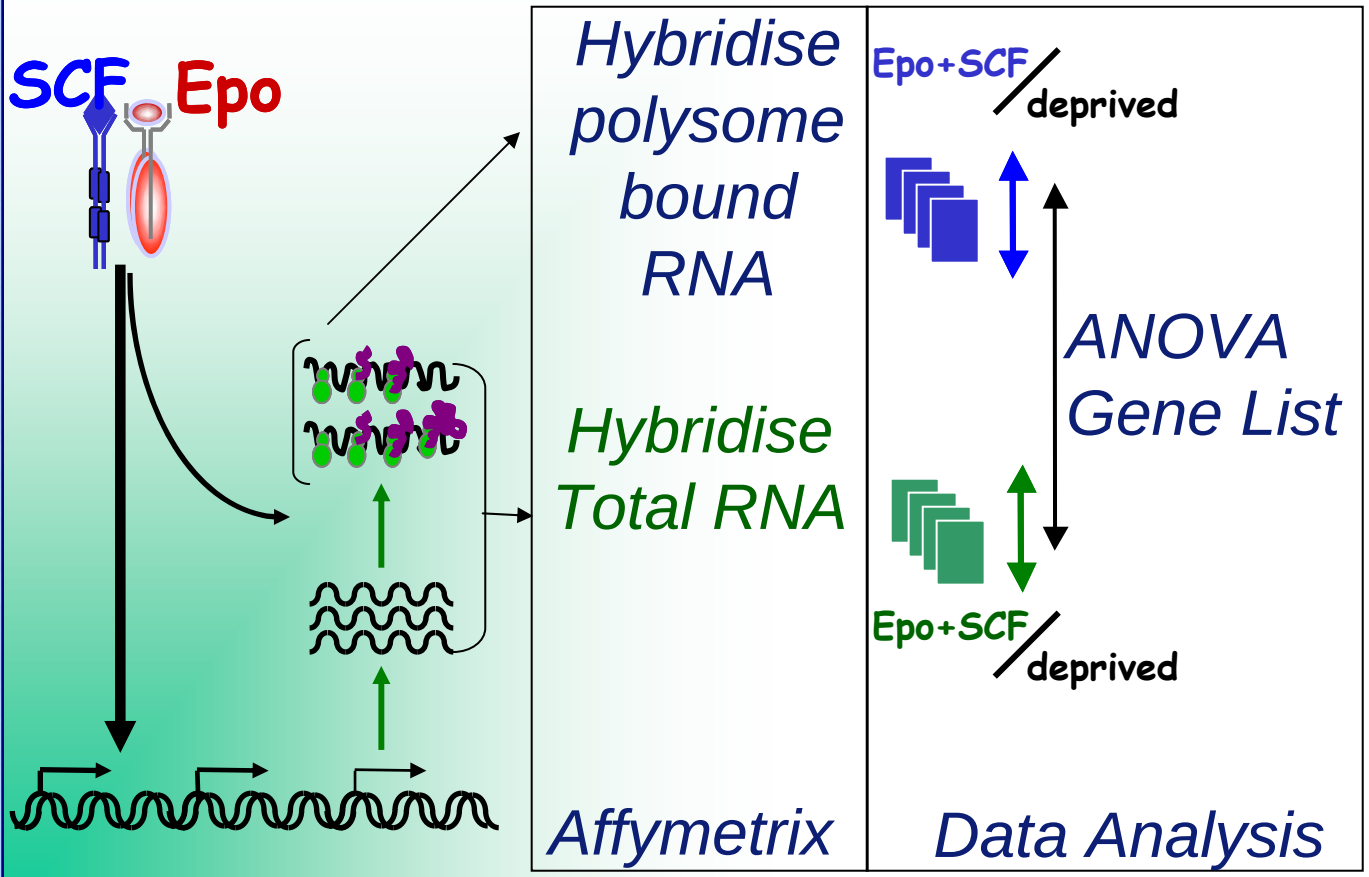
Pharmacogenetics and Personalised Medicine

Mechanism of Disease

Therapeutic targets

Biomarkers

Gene expression profiling polysome bound vs Total mRNA



Erasmus MC
University Medical Center Rotterdam

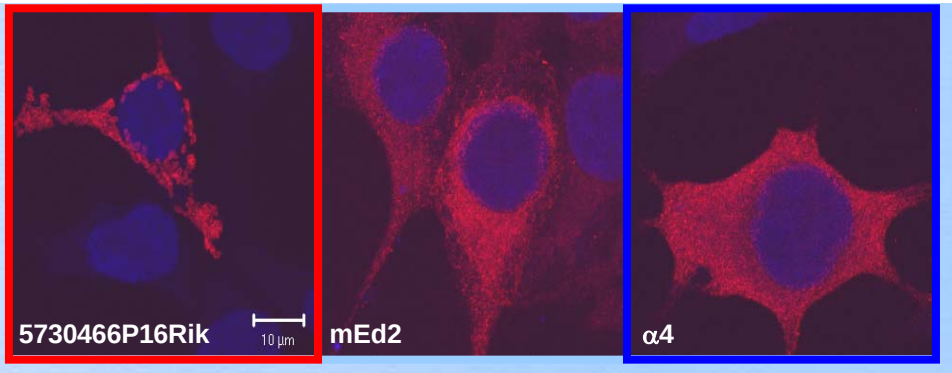
3rd Annual Course

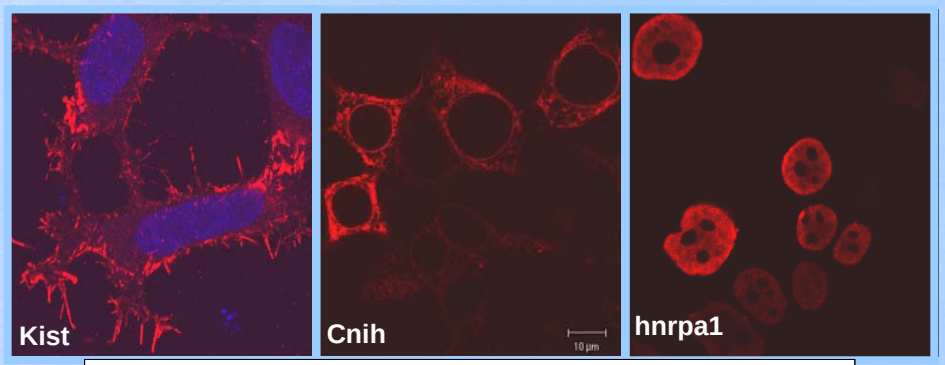
Pharmacogenetics and Personalised Medicine

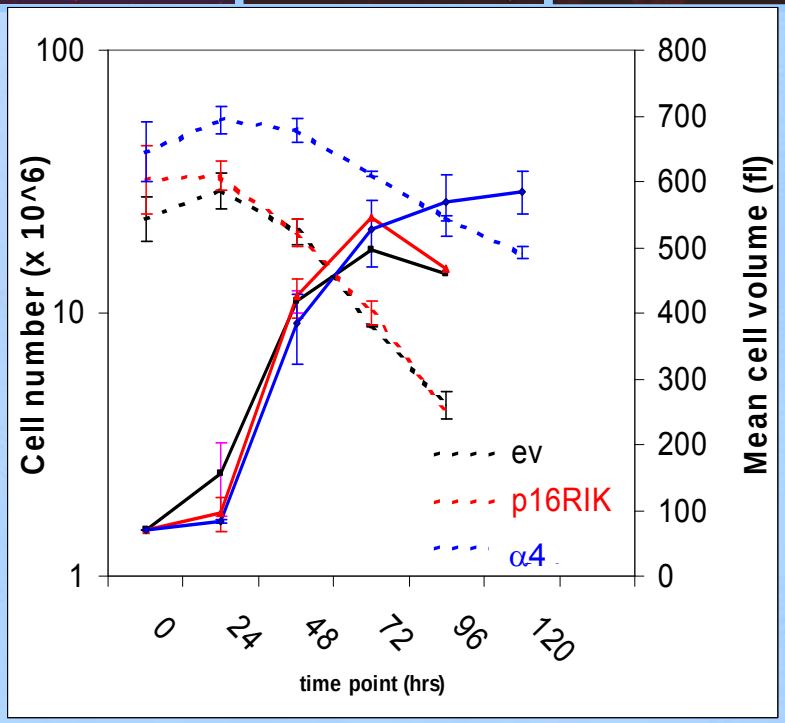
Mechanism of Disease

Therapeutic targets

Biomarkers







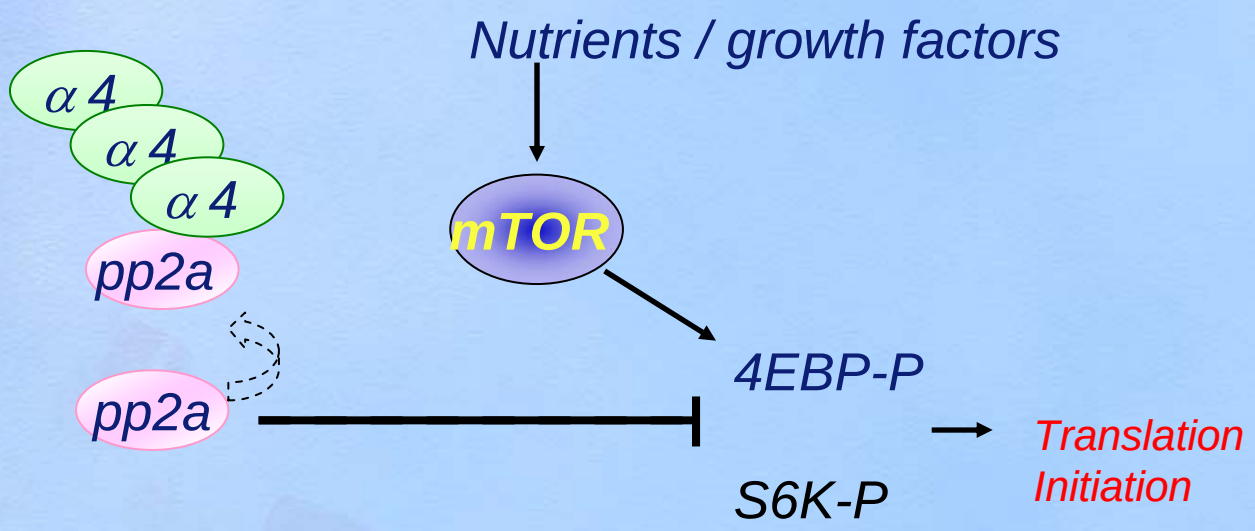
3rd Annual Course

Pharmacogenetics and Personalised Medicine

Mechanism of Disease

Therapeutic targets

Biomarkers



3rd Annual Course

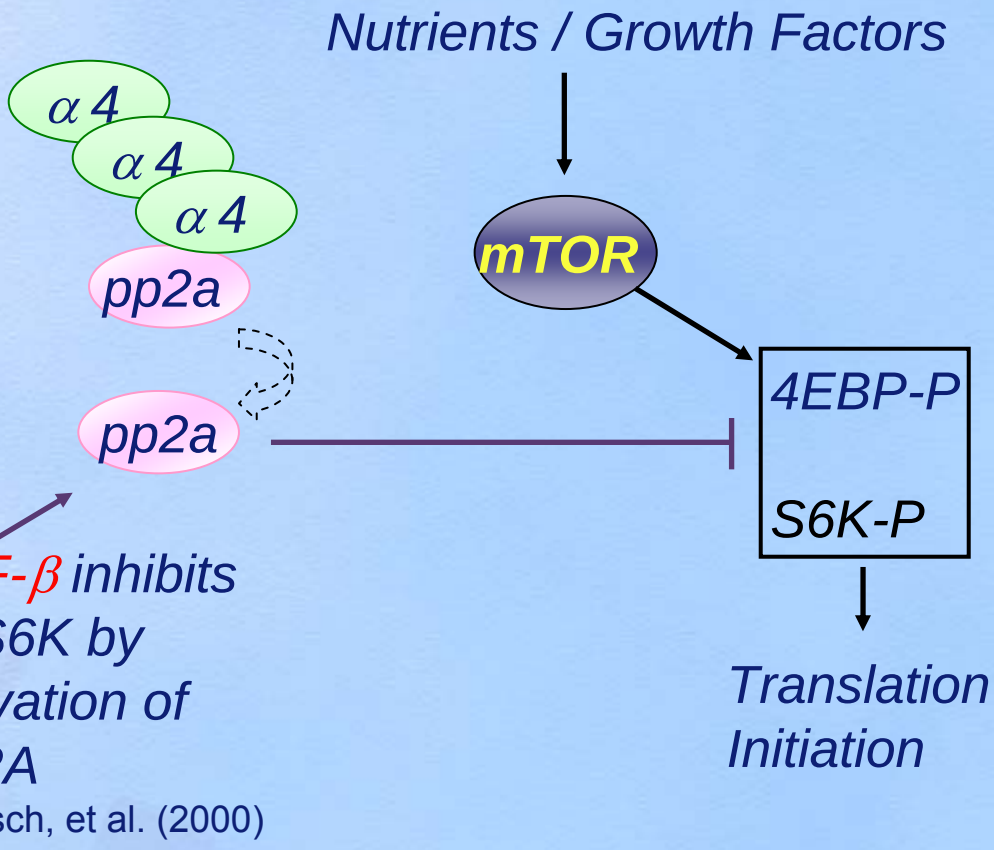
Pharmacogenetics and Personalised Medicine

Mechanism of Disease

Therapeutic targets

Biomarkers

Grech, G., et al. (**2008)**
Blood Oct 1;112(7):2750-60.



TGF-β rescues block of differentiation

FTY720 activates pp2a resulting in the release of differentiation block by Stem Cell Factor.

Neville Borg, 2009

unpublished data

3rd Annual Course

Pharmacogenetics and Personalised Medicine

Mechanism of Disease

Therapeutic targets

Biomarkers

Genomics utilised to study mechanism of disease

Identification of potential therapeutic targets

Genomics used to stratify patients into subtypes

Biomarkers used as classifiers of specific therapeutic groups

3rd Annual Course

Pharmacogenetics and Personalised Medicine

Mechanism of Disease

Therapeutic targets

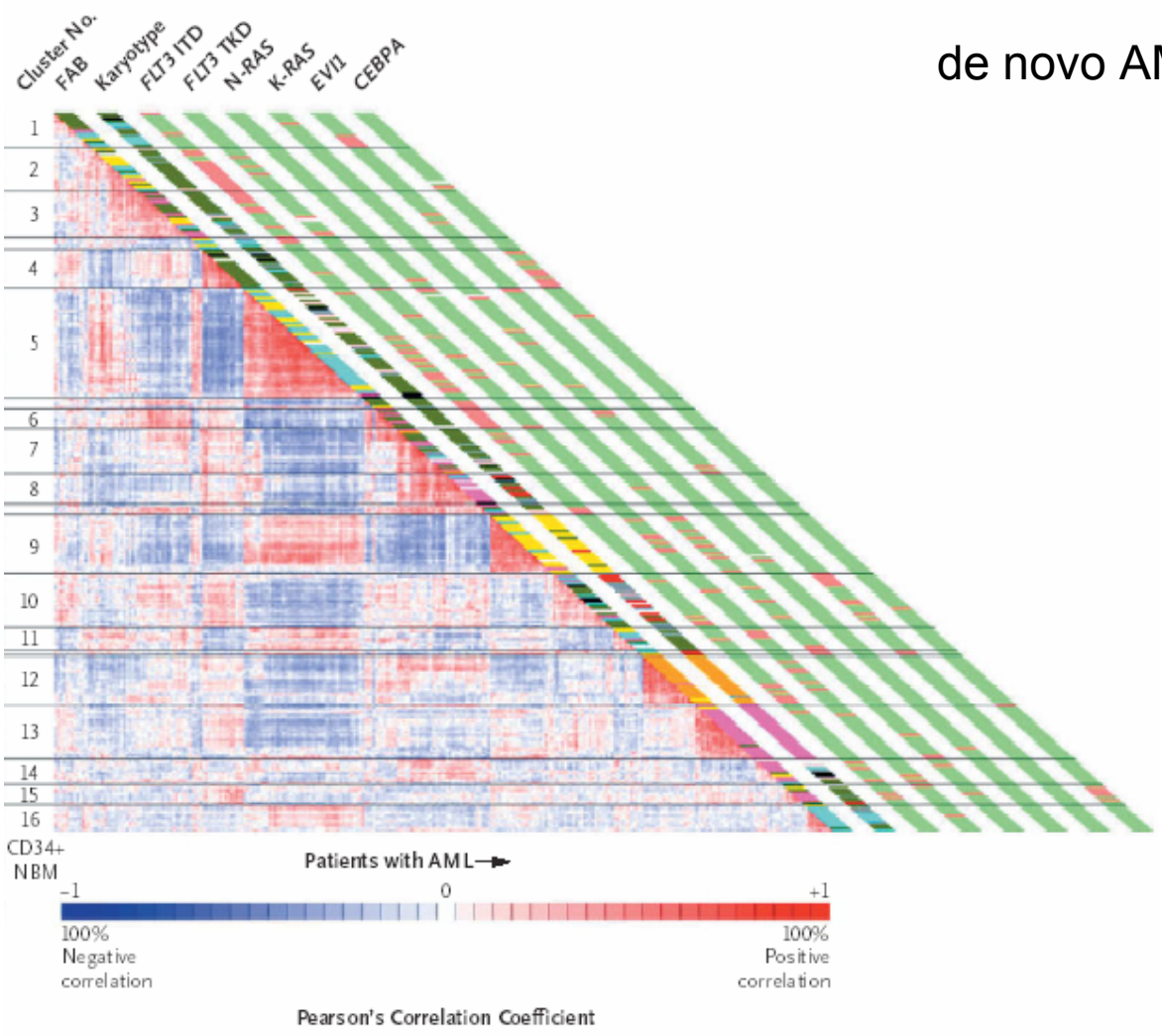
Biomarkers

Valk P.J.M., et al.
N Eng J Med 350;16 April 15, 2004

Genomics used to stratify patients into subtypes

Biomarkers used as classifiers of specific therapeutic groups

de novo AML



3rd Annual Course

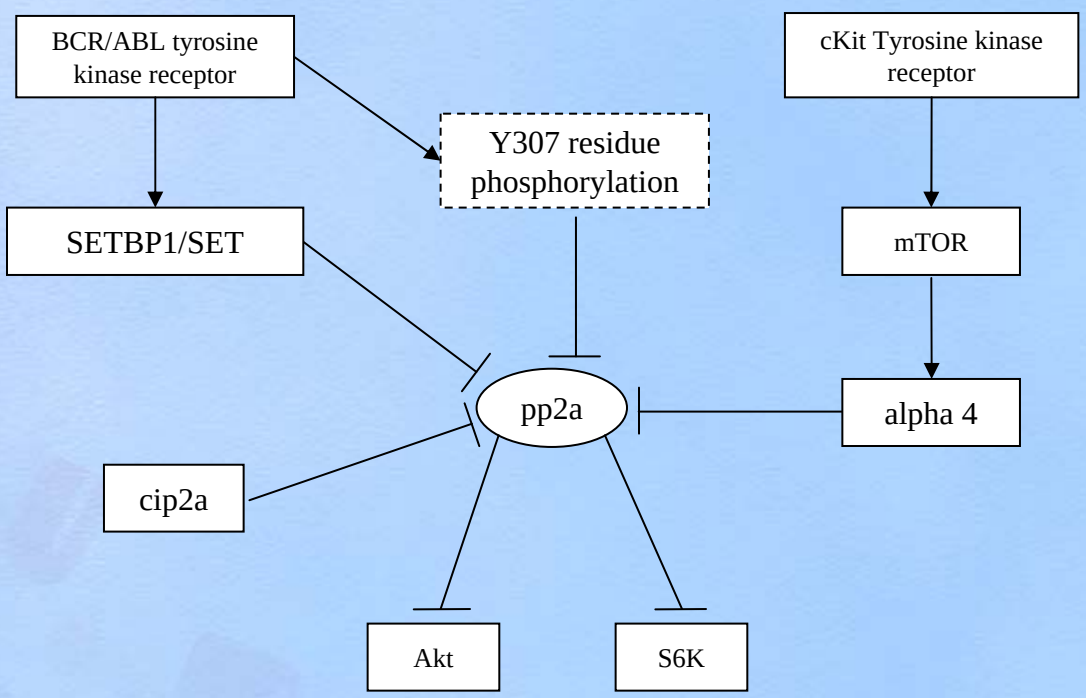
Pharmacogenetics and Personalised Medicine

Mechanism of Disease

Therapeutic targets

Biomarkers

Regulators of pp2a activity



3rd Annual Course

Pharmacogenetics and Personalised Medicine

Mechanism of Disease

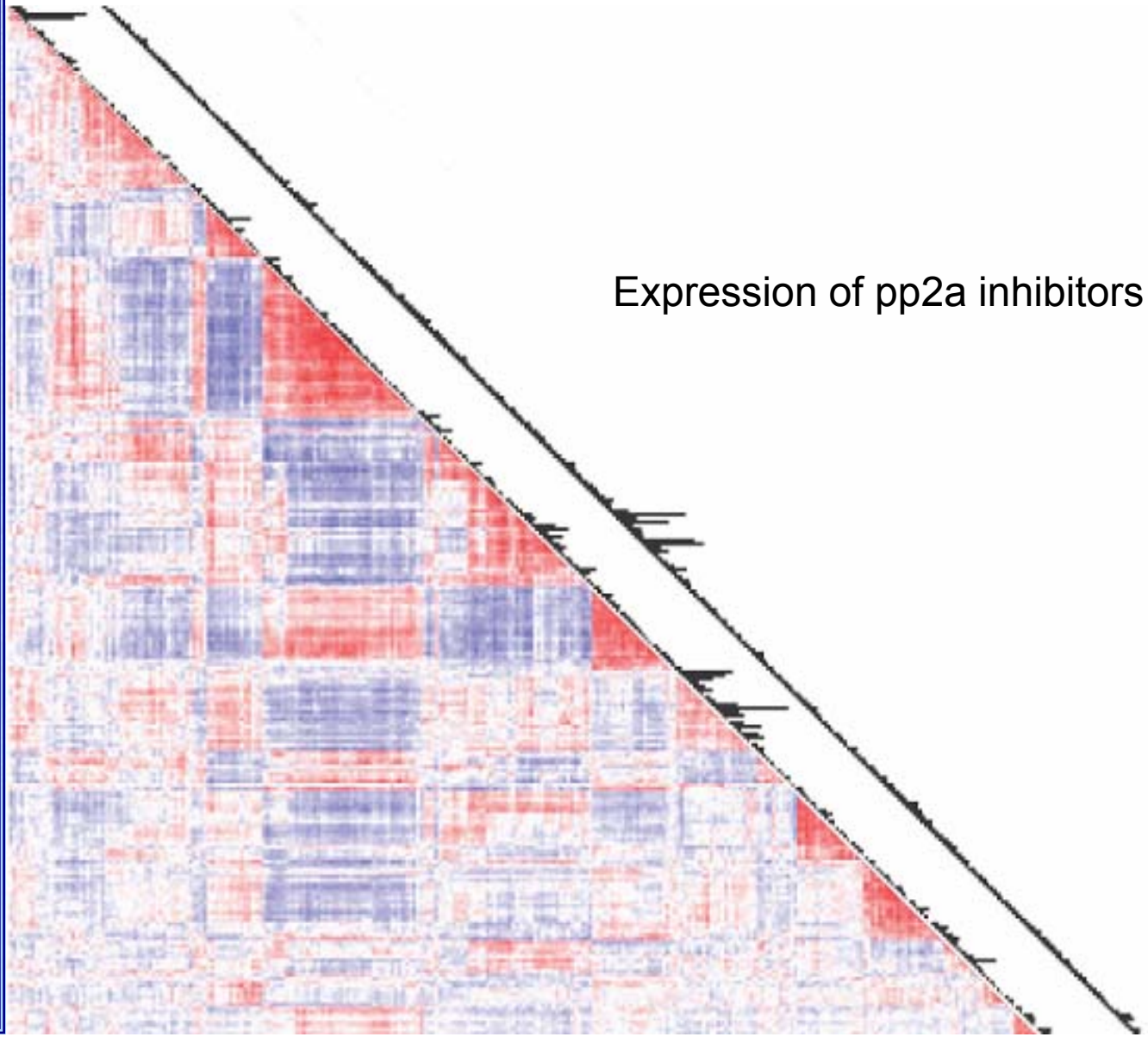
Therapeutic targets

Biomarkers

Erasmus MC
University Medical Center Rotterdam

Regulators of pp2a activity

SETBP1 CIP2A



Expression of pp2a inhibitors

3rd Annual Course

Pharmacogenetics and Personalised Medicine

Mechanism of Disease

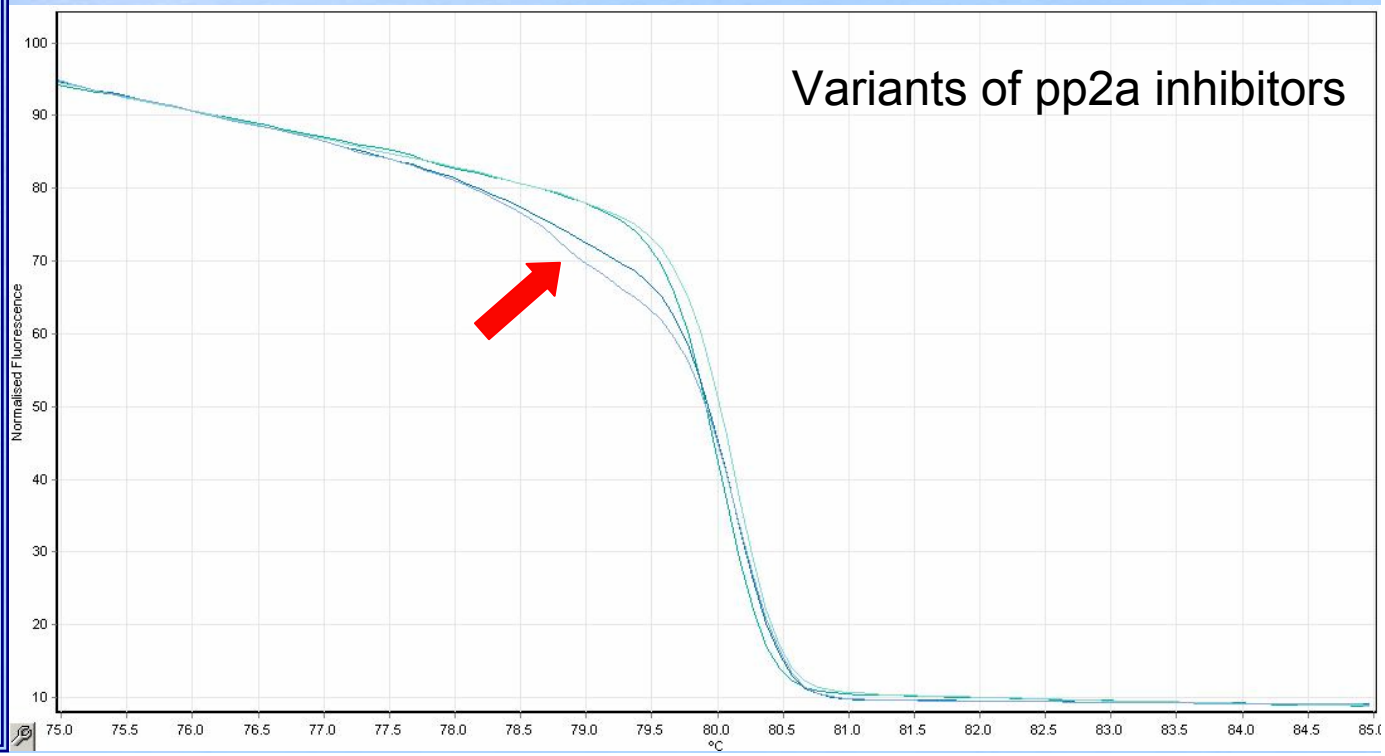
Therapeutic targets

Biomarkers

Regulators of pp2a activity

High Resolution Melting (HRM) Analysis

- Screening for coding sequence variations
- Characterisation of isoforms



Mechanism of Disease

Therapeutic targets

Biomarkers

Conclusions

- High expression of SETBP1 in a subtype of de novo AML
- Mutations were identified in myeloid cell lines in the pp2a regulators, Igbp1 and SET
- Genomics approach to classify and identify therapeutic groups sensitive to pp2a activators

.

3rd Annual Course

Pharmacogenetics and Personalised Medicine

Thank you

Dr Christian Saliba
PostDoc

Norman Formosa
Sephora Aquilina
Stephanie Gauci
Victoria Borg
Mareh Dalal
Shawn Baldacchino
Pierre Ellul
Neville Azzopardi

Marieke von Lindern
Ruud Delwel
Peter Valk
Roberto Avellino
Erasmus Medical Centre

Bridget Ellul
Head of Department

James DeGaetano
Sharon Falzon
Mater Dei Hospital

Neville Borg
Nigel Borg
Mareh Dalal
MSc students

Shawn Baldacchino
PhD student