Targeting isoforms of PI 3-kinase in cancer

our laboratory ☺

Bart Vanhaesebroeck

UCL Cancer Institute
London - UK

16th ASEICA International Congress

VALENCIA – Nov 2018

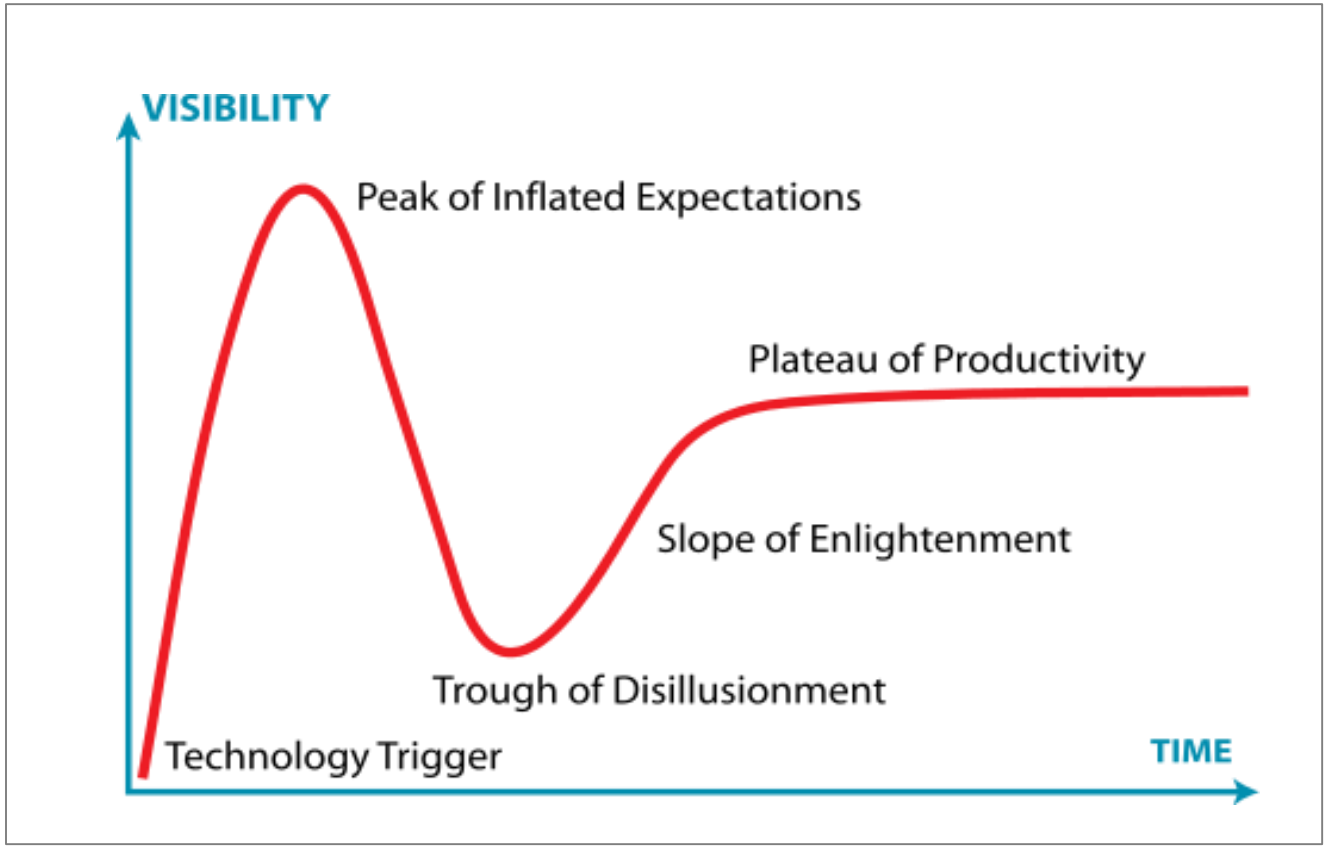
Bart Vanhaesebroeck

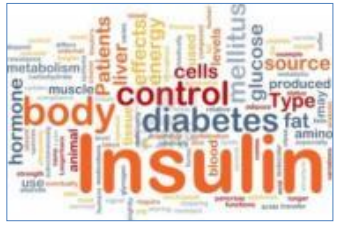
Disclosure Information

- **Karus Therapeutics** (Oxford, UK) – SAB & Stockholder
- **iOnctura** (Geneva, Switzerland) – SAB
- **Gilead** - Speakers fees
- **hVIVO** (London, UK) – Stockholder

TARGETED CANCER THERAPIES

- where are we on the hype curve? -

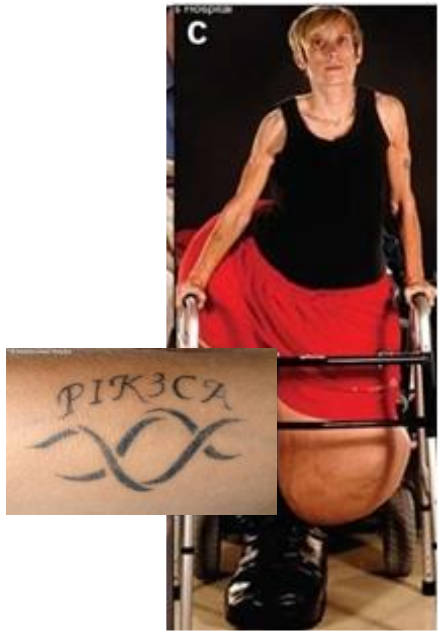




METABOLIC DISEASE

CANCER

INFLAMMATION & AUTO-IMMUNITY
(inc. arthritis, asthma, …)

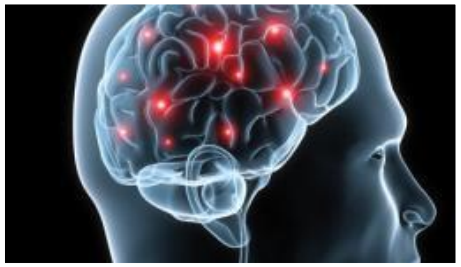


OVERGROWTH SYNDROMES

PI3K
in human health & disease
- 2018 -

CARDIOVASCULAR DISEASE

AGEING

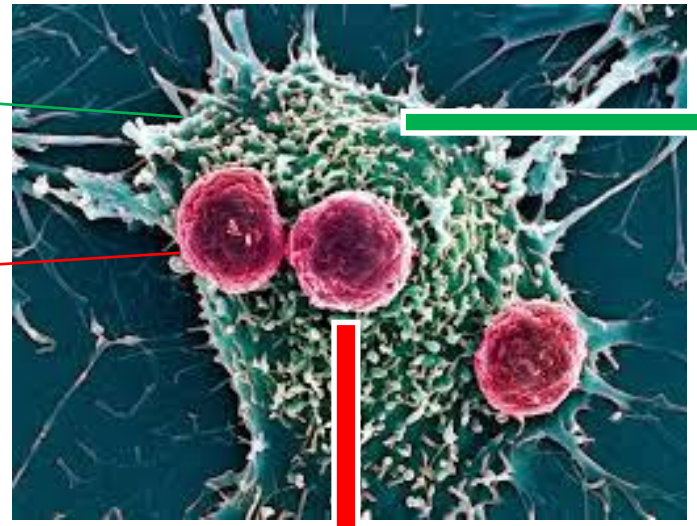


NEUROBIOLOGY (eg epilepsia)

Targeting PI3K in cancer

CANCER CELL

WHITE BLOOD CELL



‘Traditional’ approach:

blocking PI3K in the cancer cell

↓

cytostasis/cytotoxicity?

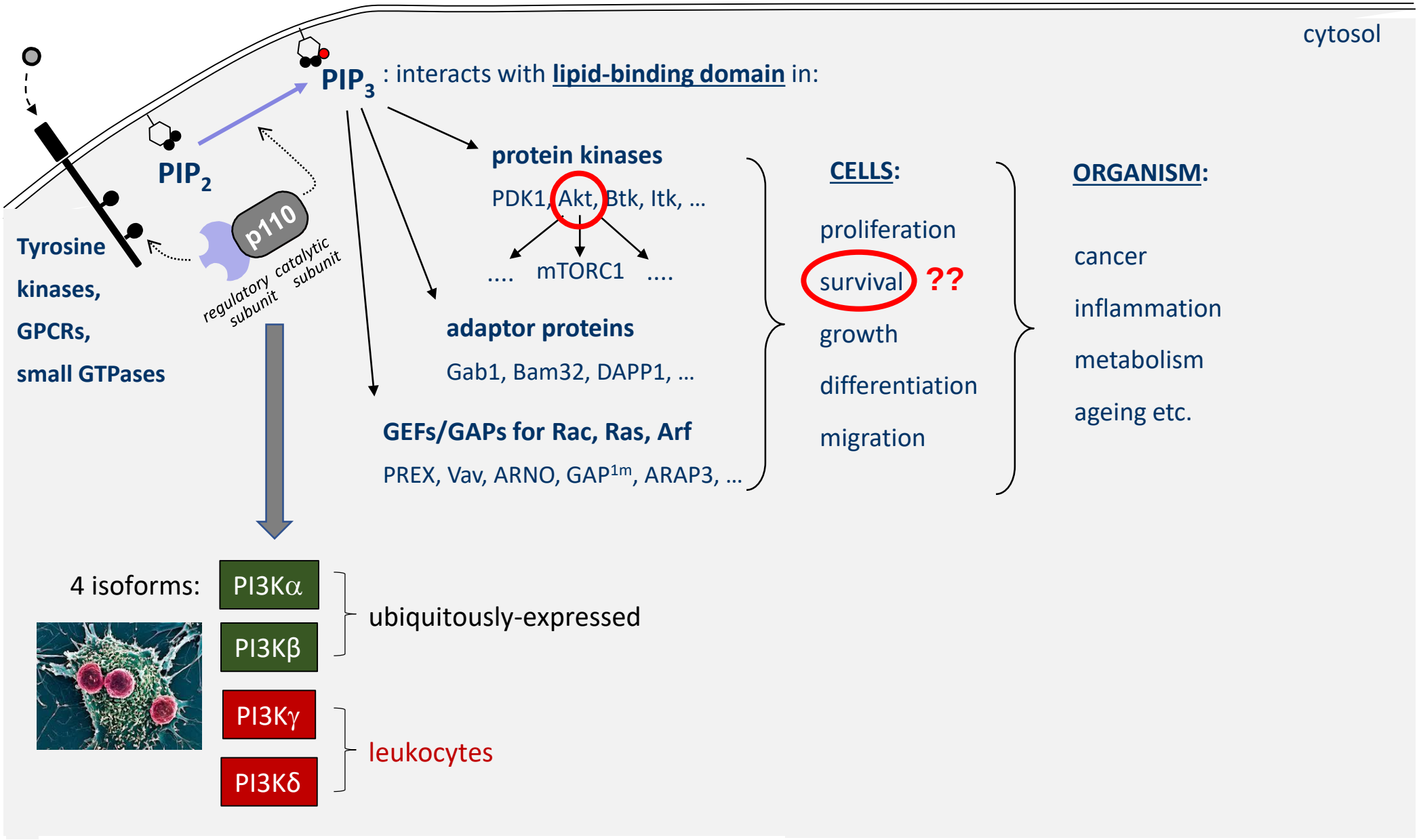
‘different’ approach:

blocking PI3K in immune cells

↓

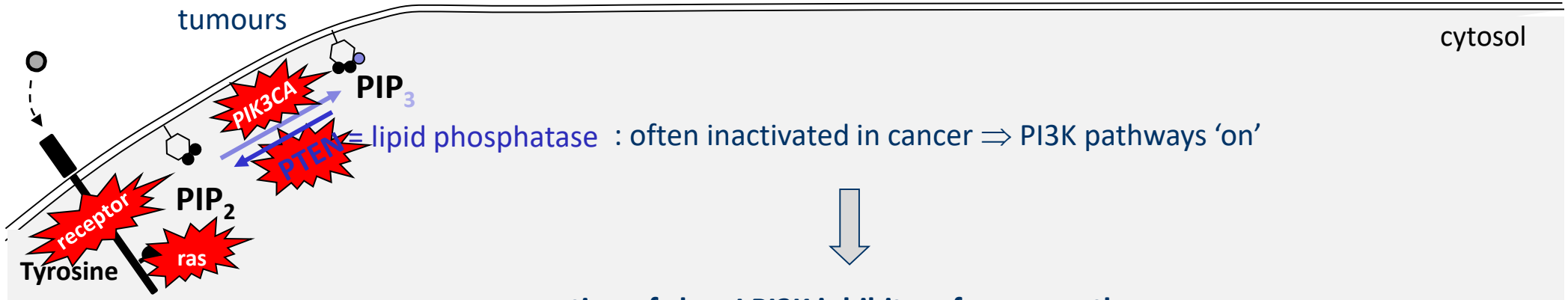
cancer immunotherapy?

Class I PI3K signalling



Class I PI3K signalling in cancer

PI3Kα mutations are very frequent in solid tumours

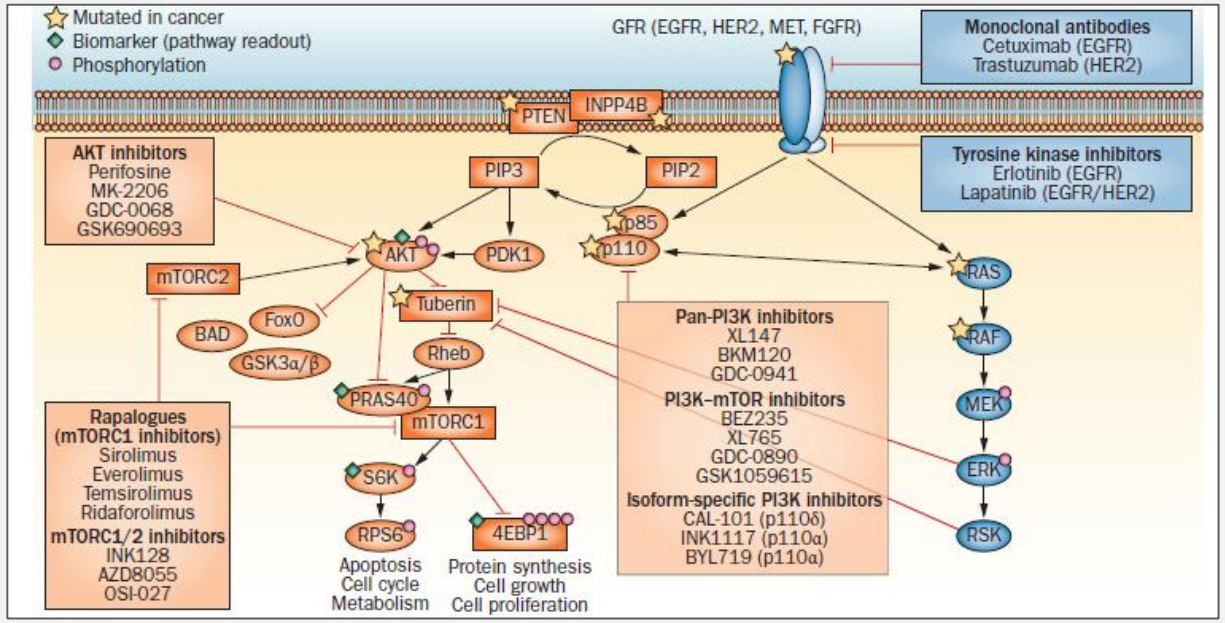


Tyrosine kinases, GPCRs, small GTPases

≡ lipid phosphatase : often inactivated in cancer ⇒ PI3K pathways 'on'

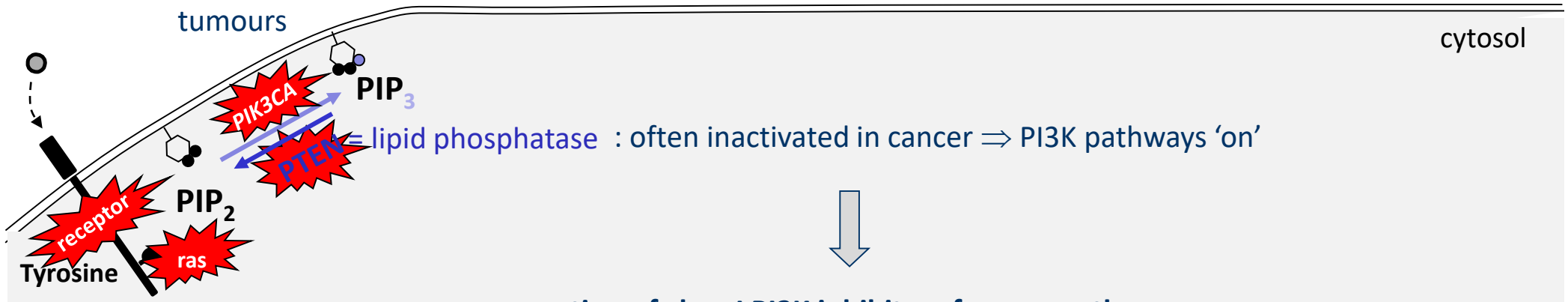
generation of class I PI3K inhibitors for cancer therapy

- targeting individual or groups of class I PI3Ks -



Class I PI3K signalling in cancer

PI3Kα mutations are very frequent in solid tumours



Tyrosine kinases, GPCRs, small GTPases

PTEN = lipid phosphatase : often inactivated in cancer ⇒ PI3K pathways 'on'

⇓

generation of class I PI3K inhibitors for cancer therapy

- targeting individual or groups of class I PI3Ks -

	activating mutations in cancer:		
PI3Kα	+++	ubiquitously-expressed	- SOLID TUMOURS
PI3Kβ	±		
PI3Kγ	–	leukocytes	- HAEM-ONC - IMMUNE-INFLAMM
PI3Kδ	±		

development of class I PI3K inhibitors for cancer therapy

- targeting individual or groups of class I PI3Ks -

thus far: modest impact in solid tumours

- if effect: mainly cytostatic
- insufficient PI3K target coverage
- issues with drug tolerability
- drug resistance
  - intrinsic : negative feedback loops are very common
  - acquired genetic resistance is common
- cells can live with very little PI3K activity
- PI3K mutations can be early (clonal) or late (subclonal) in tumour evolution

↓

'smart' combination therapies will be required

eg: **PI3Kα inhibitor-mediated sensitization of breast cancer to hormone therapy**

Estrogen receptor (ER)-positive breast cancer + **PI3Kα inhibitor**

↓

ER transcriptional activity ↑

↓

sensitize breast cancer to hormone therapy

development of class I PI3K inhibitors for cancer therapy

- targeting individual or groups of class I PI3Ks -

thus far: modest impact in solid tumours

- if effect: mainly cytostatic
- insufficient PI3K target coverage
- issues with drug tolerability
- drug resistance
  - intrinsic : negative feedback loops are very common
  - acquired genetic resistance is common
- cells can live with very little PI3K activity
- PI3K mutations can be early (clonal) or late (subclonal) in tumour evolution

↓

'smart' combination therapies will be required

24 AUGUST 2018 NEWS

Novartis reports positive results from SOLAR-1 trial

PI3Kα inhibitor = BYL719

Novartis has reported positive results from the SOLAR-1 trial after the study met its primary endpoint.

The global trial is a Phase III, randomised, double-blind, placebo-controlled study evaluating BYL719 (alpelisib) in combination with fulvestrant against fulvestrant alone for the treatment of post-menopausal women.

development of class I PI3K inhibitors for cancer therapy

- targeting individual or groups of class I PI3Ks -

24 AUGUST 2018 NEWS

Novartis reports positive results from SOLAR-1 trial

PI3Kα inhibitor = BYL719

Novartis has reported positive results from the SOLAR-1 trial after the study met its primary endpoint.

The global trial is a Phase III, randomised, double-blind, placebo-controlled study evaluating BYL719 (alpelisib) in combination with fulvestrant against fulvestrant alone for the treatment of post-menopausal women.

activating mutations in cancer:

PI3Kα	+++	ubiquitously-expressed	- SOLID TUMOURS
PI3Kβ	±		
PI3Kγ	–	leukocytes	- HAEM-ONC - IMMUNE-INFLAMM
PI3Kδ	±		

?

FDA-approved PI3K-inhibitors: for B-cell malignancies

- **idelalisib**: PI3Kδ (Gilead)
- **copanlisib**: PI3Kα/δ (Bayer)
- **duvelisib**: PI3Kγ/δ (Verastem)

Idelalisib
FDA/EMA approval in 2014

Copanlisib
FDA approval in 2017

Duvelesib
FDA approval in 2018

PI3Kδ

in normal physiology

PI3Kδ 2004

p110δ, a novel phosphoinositide 3-kinase in leukocytes

BART VANHAESEBROECK*, MELANIE J. WELHAM†, KEI KOTANI*, ROB STEIN*, PATRICIA H. WARNE‡, MARKÉTA J. ZVELEBIL*, KYOICHIRO HIGASHI*, STEFANO VOLINIA§, JULIAN DOWNWARD‡, AND MICHAEL D. WATERFIELD¶||

PNAS 1997:94:4330

Impaired B and T Cell Antigen Receptor Signaling in p110δ PI 3-Kinase Mutant Mice

Klaus Okkenhaug,[1] Antonio Bilancio,[1*] Géraldine Farjot,[1*] Helen Priddle,[2*†] Sara Sancho,[3] Emma Peskett,[1] Wayne Pearce,[1] Stephen E. Meek,[2] Ashreena Salpekar,[1] Michael D. Waterfield,[1,4] Andrew J. H. Smith,[2] Bart Vanhaesebroeck[1,4‡]

Science 2002:297:1031

Essential role for the p110δ phosphoinositide 3-kinase in the allergic response

Khaled Ali[1,2], Antonio Bilancio[1], Matthew Thomas[3], Wayne Pearce[1], Alasdair M. Gilfillan[4], Christine Tkaczyk[4], Nicolas Kuehn[5], Alexander Gray[6], June Giddings[3], Emma Peskett[1], Roy Fox[3], Ian Bruce[3], Christoph Walker[3], Carol Sawyer[1*], Klaus Okkenhaug[1*], Peter Finan[3] & Bart Vanhaesebroeck[1,2]

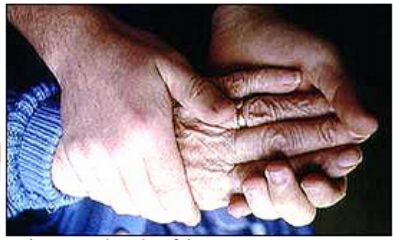
Nature 2004:431:1007

BBC NEWS

You are in: Health

Thursday, 18 July, 2002, 19:11 GMT 20:11 UK

Hope for arthritis breakthrough



Arthritis is a disorder of the immune system

Scientists believe they may have discovered the key to new treatments for arthritis.

A team from University College London has uncovered a molecule that appears to play a central role in triggering the immune system response that causes the condition.

They believe the discovery may also ultimately lead to new ways to tackle other immune system disease, leukaemia, and transplant rejection.

The study forms part of an ongoing effort to better understand how signalling systems inside cells are controlled by PI3-kinase - a group of enzymes with a known link to cancer.

> "You could potentially design a medicine that hits the immune system quite hard"
>
> Dr Bart Vanhaesebroeck

Under normal circumstances, PI3-kinase affects the growth, movement and survival of cells.

But if not kept in check, the same signalling can cause tumours.

The UCL scientists genetically engineered mice in whom one of the P13-kinase enzymes, called p110delta, was switched off.

BBC NEWS — LIVE — BBC NEWS CHANNEL

Last Updated: Friday, 15 February 2008, 17:09 GMT

E-mail this to a friend — Printable version

Molecule 'triggers allergy attack'

The discovery of a molecule which appears to play a key role in allergies may lead to new therapies, experts say.

Allergies have trebled in 20 years

The researchers from Barts and the London School of Medicine managed to stop allergic attacks in mice by targeting the molecule, P110delta.

They say it may offer the chance to prevent allergies, not just relieve symptoms.

The Journal of Immunology reported that the method did not interfere with the rest of the body's immune defences.

Allergies happen when part of the immune system identifies something common and harmless, such as pollen or house mite faeces, as a foreign invader, and launches an attack.

> "We are very hopeful that a drug for human patients can be developed in the very near future"
>
> Professor Bart Vanhaesebroeck
> Barts and The London School of Medicine

Unfortunately, this can cause inflammation on the skin, in the nose or airways, which creates the unpleasant and sometimes dangerous symptoms reported by sufferers.

Most anti-allergy pills can reduce the symptoms, but scientists cannot shut down the process itself without damping down the entire immune system, and making the person vulnerable to genuine threats such as infection.

So they are looking in more detail at the chain reaction of an allergy attack, looking for new ways to target the causes more precisely.

'Take control

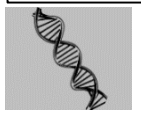
The London-based team were looking at a family of proteins called PI3Ks, which have a variety of roles around the body. The P110delta molecule is one of these.

PI3Kδ 2004

p110δ, a novel phosphoinositide 3-kinase in leukocytes

Bart Vanhaesebroeck*, Melanie J. Welham†, Kei Kotani*, Rob Stein*, Patricia H. Warne‡, Markéta J. Zvelebil*, Kyoichiro Higashi*, Stefano Volinia§, Julian Downward‡, and Michael D. Waterfield¶||

PNAS 1997:94:4330



Impaired B and T Cell Antigen Receptor Signaling in p110δ PI 3-Kinase Mutant Mice

Klaus Okkenhaug,[1] Antonio Bilancio,[1*] Géraldine Farjot,[1*] Helen Priddle,[2*†] Sara Sancho,[3] Emma Peskett,[1] Wayne Pearce,[1] Stephen E. Meek,[2] Ashreena Salpekar,[1] Michael D. Waterfield,[1,4] Andrew J. H. Smith,[2] Bart Vanhaesebroeck[1,4‡]

Science 2002:297:1031

Essential role for the p110δ phosphoinositide 3-kinase in the allergic response

Khaled Ali[1,2], Antonio Bilancio[1], Matthew Thomas[3], Wayne Pearce[1], Alasdair M. Gilfillan[4], Christine Tkaczyk[4], Nicolas Kuehn[5], Alexander Gray[6], June Giddings[3], Emma Peskett[1], Roy Fox[3], Ian Bruce[3], Christoph Walker[3], Carol Sawyer[1*], Klaus Okkenhaug[1*], Peter Finan[3] & Bart Vanhaesebroeck[1,2]

Nature 2004:431:1007

PI3Kδ : mainly adaptive immune phenotypes (B/T-cells)

PI3Kγ : mainly innate immunity

⇩

drug targets in immune/inflamm diseases

⇩

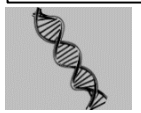
development of PI3Kγ/δ inhibitors

PI3Kδ 2018

p110δ, a novel phosphoinositide 3-kinase in leukocytes

Bart Vanhaesebroeck*, Melanie J. Welham†, Kei Kotani*, Rob Stein*, Patricia H. Warne‡, Markéta J. Zvelebil*, Kyoichiro Higashi*, Stefano Volinia§, Julian Downward‡, and Michael D. Waterfield¶||

PNAS 1997:94:4330



Impaired B and T Cell Antigen Receptor Signaling in p110δ PI 3-Kinase Mutant Mice

Klaus Okkenhaug,[1] Antonio Bilancio,[1*] Géraldine Farjot,[1*] Helen Priddle,[2*†] Sara Sancho,[3] Emma Peskett,[1] Wayne Pearce,[1] Stephen E. Meek,[2] Ashreena Salpekar,[1] Michael D. Waterfield,[1,4] Andrew J. H. Smith,[2] Bart Vanhaesebroeck[1,4‡]

Science 2002:297:1031

Essential role for the p110δ phosphoinositide 3-kinase in the allergic response

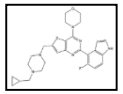
Khaled Ali[1,2], Antonio Bilancio[1], Matthew Thomas[3], Wayne Pearce[1], Alasdair M. Gilfillan[4], Christine Tkaczyk[4], Nicolas Kuehn[5], Alexander Gray[6], June Giddings[3], Emma Peskett[1], Roy Fox[3], Ian Bruce[3], Christoph Walker[3], Carol Sawyer[1*], Klaus Okkenhaug[1*], Peter Finan[3] & Bart Vanhaesebroeck[1,2]

Nature 2004:431:1007

PI3Kδ : mainly adaptive immune phenotypes (B/T-cells)

PI3Kδ : drug targeting

PIRAMED PHARMA → Roche



(2008: *together with PI3Kα programme)*

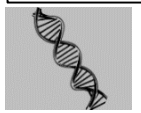
- **ICOS → Calistoga → Gilead**
- **Intellikine → Infinity → Verastem**
- **Amgen → CRUK**
- **Xelexis → Merck**
- **GSK:** inhaled PI3Kδ inhibitor
- **TG Therapeutics**
- **Incyte**
- **Merck AG→ iOnctura**
- **Novartis :** activated PI3Kδ syndrome
- **UCB**
- **Chi-Med**
- **MEI Pharma**
- **various academic groups e.g. Puquitinib**

PI3Kδ 2004

p110δ, a novel phosphoinositide 3-kinase in leukocytes

Bart Vanhaesebroeck*, Melanie J. Welham†, Kei Kotani*, Rob Stein*, Patricia H. Warne‡, Markéta J. Zvelebil*, Kyoichiro Higashi*, Stefano Volinia§, Julian Downward‡, and Michael D. Waterfield¶||

PNAS 1997:94:4330



Impaired B and T Cell Antigen Receptor Signaling in p110δ PI 3-Kinase Mutant Mice

Klaus Okkenhaug,[1] Antonio Bilancio,[1*] Géraldine Farjot,[1*] Helen Priddle,[2*†] Sara Sancho,[3] Emma Peskett,[1] Wayne Pearce,[1] Stephen E. Meek,[2] Ashreena Salpekar,[1] Michael D. Waterfield,[1,4] Andrew J. H. Smith,[2] Bart Vanhaesebroeck[1,4‡]

Science 2002:297:1031

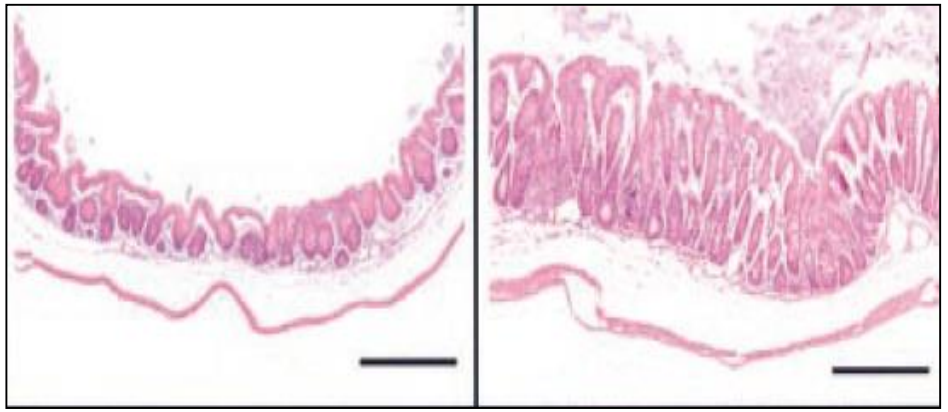
Essential role for the p110δ phosphoinositide 3-kinase in the allergic response

Khaled Ali[1,2], Antonio Bilancio[1], Matthew Thomas[3], Wayne Pearce[1], Alasdair M. Gilfillan[4], Christine Tkaczyk[4], Nicolas Kuehn[5], Alexander Gray[6], June Giddings[3], Emma Peskett[1], Roy Fox[3], Ian Bruce[3], Christoph Walker[3], Carol Sawyer[1*], Klaus Okkenhaug[1*], Peter Finan[3] & Bart Vanhaesebroeck[1,2]

Nature 2004:431:1007

one 'issue' in PI3Kδ-deficient mice:

wild-type mice | PI3Kδ kinase-dead mice



'inflammatory bowel disease'

PI3Kδ in cancer

a. cancer-cell-intrinsic roles

PI3Kδ in haem-malignancies:

in vitro **leukaemic cells**

- **PI3Kδ: highly expressed:**
  - ≈ levels as in untransformed leukocytes: not overexpressed or mostly non-mutated
- **PI3Kδ-inhibitors: PI3K→ Akt → survival?**
  - inhibitors can wipe out cellular phospho-Akt
  - are **not directly cytotoxic**
  - **have a pro-survival role, like PI3Kα in these cells (not γ or β) →** PI3Kα/δ-inhibitor (*copanlisib, Bayer*): stronger direct anti-leukaemic activity than PI3Kδ-inhibition only

in patients **clinical impact in (only) SOME haem-onc malignancies**

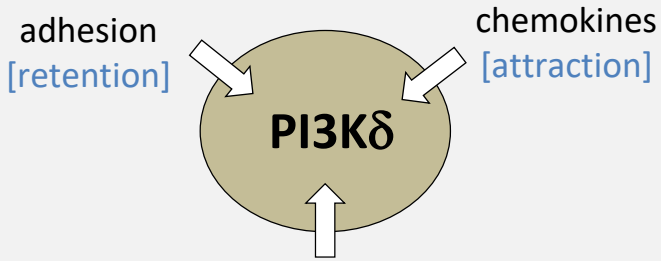
e.g. in B-cell chronic lymphocytic leukaemia (CLL) – follicular B-cell lymphoma

PI3Kδ in haem-malignancies:

Why B-cells?

PI3Kδ is an important player in:

normal B-cells



- **B-cell antigen receptor (BCR)**
  - CD40 - CD19 -
  - cytokines …

  [(co)-stimulation]

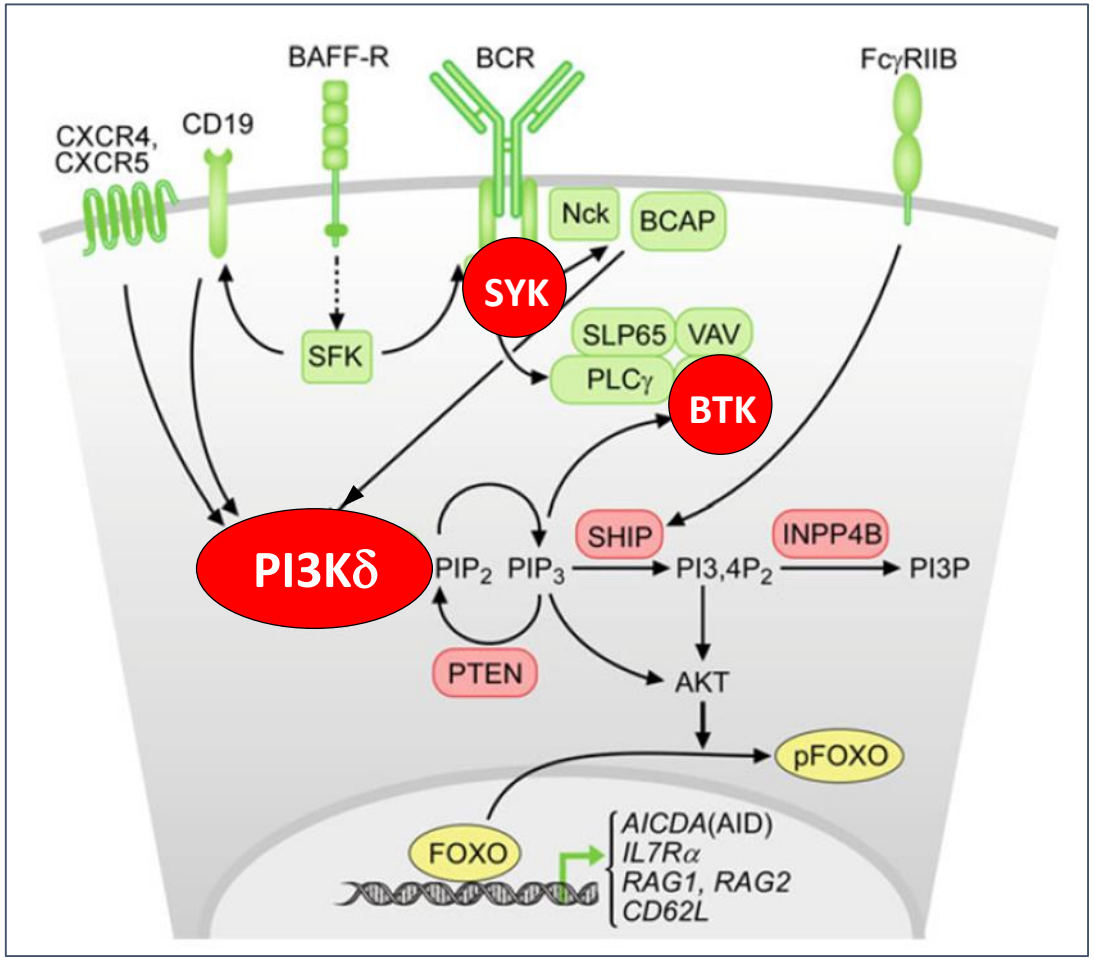
***some* B-cell malignancies (such as CLL)**

dependency on PI3Kδ is maintained, including 'tonic' BCR signalling

=

KEY VULNERABILITY

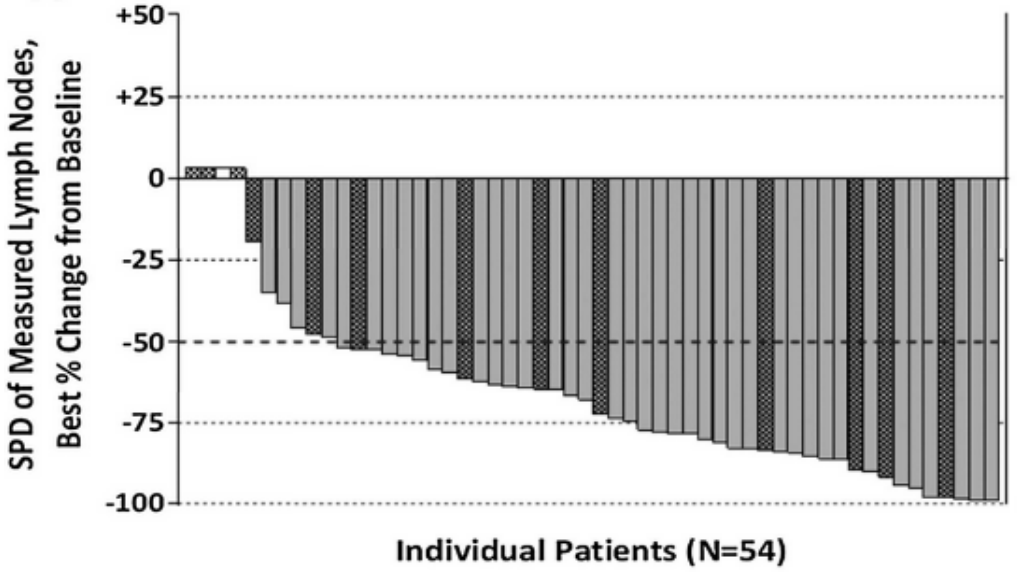
B-cell antigen receptor (BCR) signalling



Okkenhaug & Burger - *Curr Top Microbiol Immunol*. 2015:393:123

PI3Kδ in haem-malignancies:

PI3Kδ-selective inhibitor in CLL



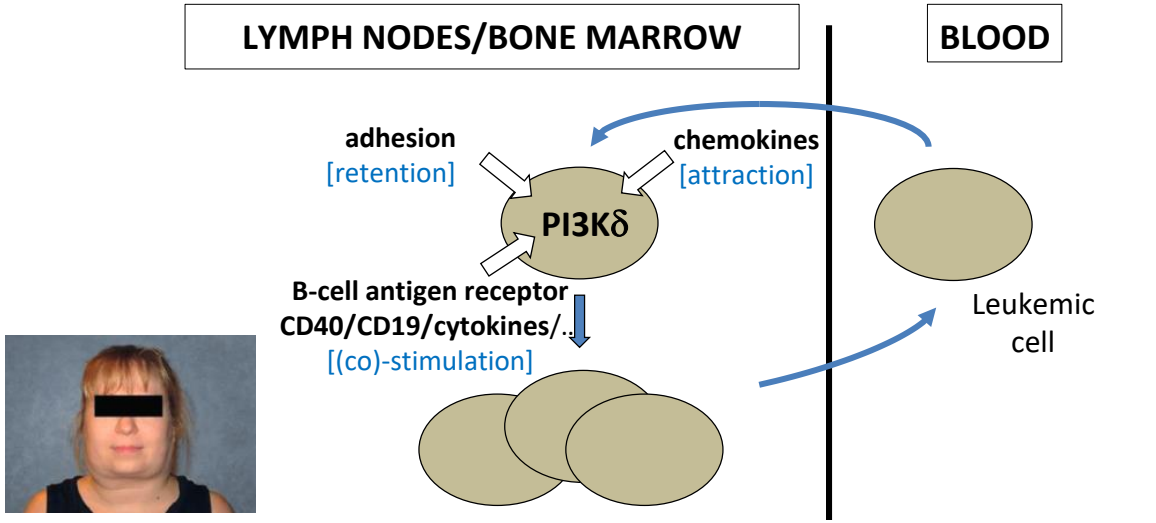
Brown JR - *Blood*. 2014 May 29;123(22):3390-7

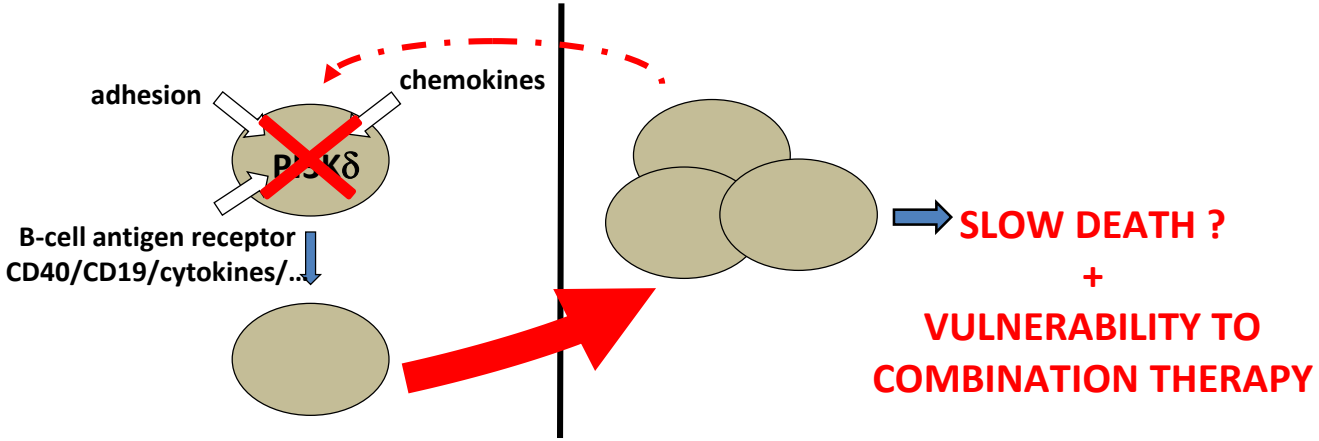
no direct cytotoxicity on CLL cells *in vitro*

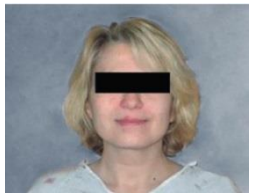
how does this drug work then ?

disrupts CLL-stroma interactions

PI3Kδ inhibition in CLL affects the malignant niche







no evidence for development of cancer cell-intrinsic PI3Kδ-inhibitor resistance
(as opposed to Btk-inhibitors)

PI3Kδ in cancer

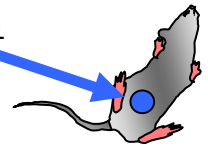
b. cancer cell-extrinsic roles

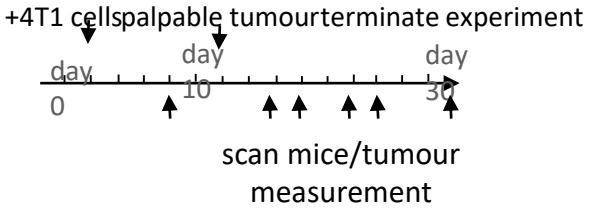
inoculate tumours (haem- or solid) in PI3Kδ-null mice:

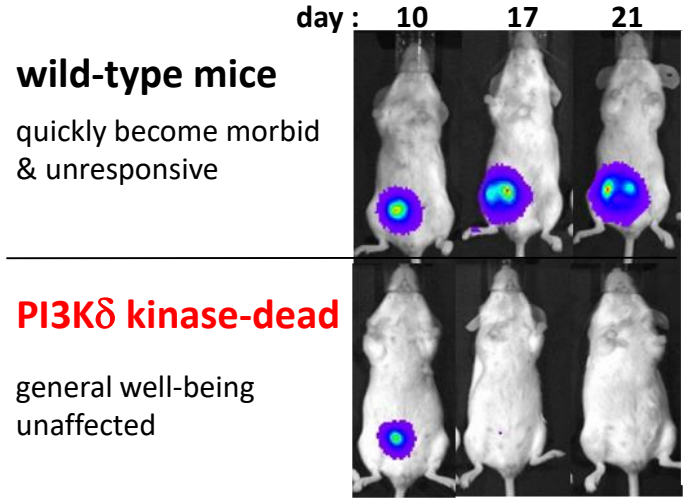
GENETICS

4T1 breast cancer (PI3Kδ-negative)

inject **luciferase**+ 4T1 breast cancer cells in mammary fat pad

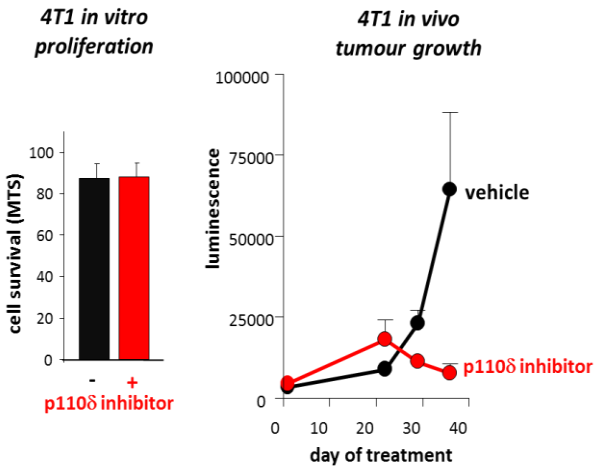


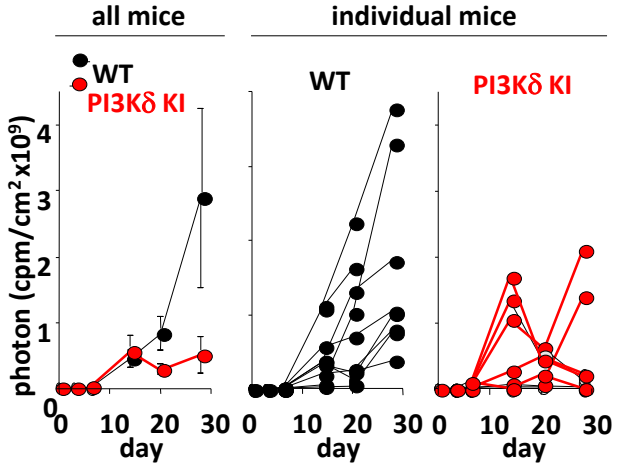




PHARMACOLOGY

pharmacological PI3Kδ inhibition
(in wild-type, immuno-competent mice)





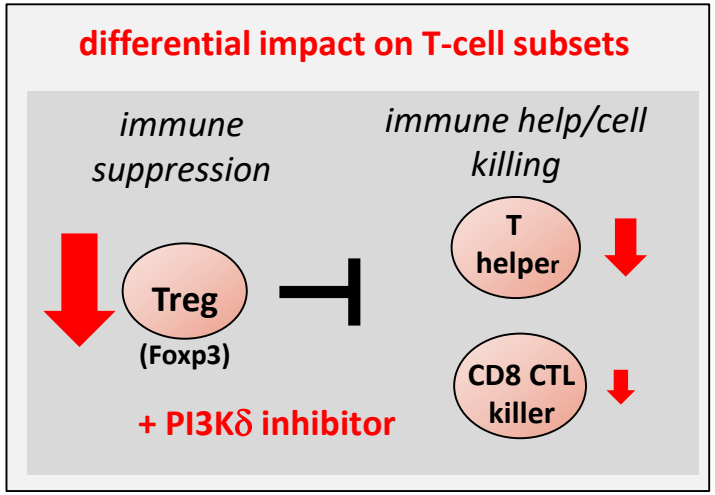
→ **does this also work in human? Head & Neck cancer window trial with Amgen & Cancer Research UK**

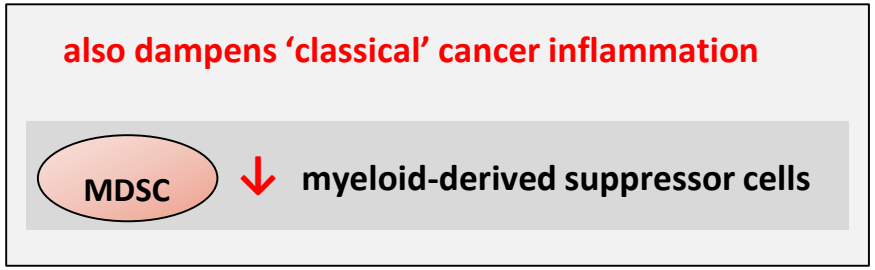
How does this work?

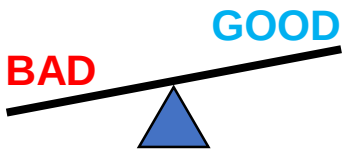
PI3Kδ inhibition re-balances the host immune system (towards ‘auto-immunity’)

How does this work?

PI3Kδ inhibition re-balances the host immune system (towards 'auto-immunity')







immune response

↑ **CD8/Treg** (Foxp3) **ratio**

immune activation through immune suppression….

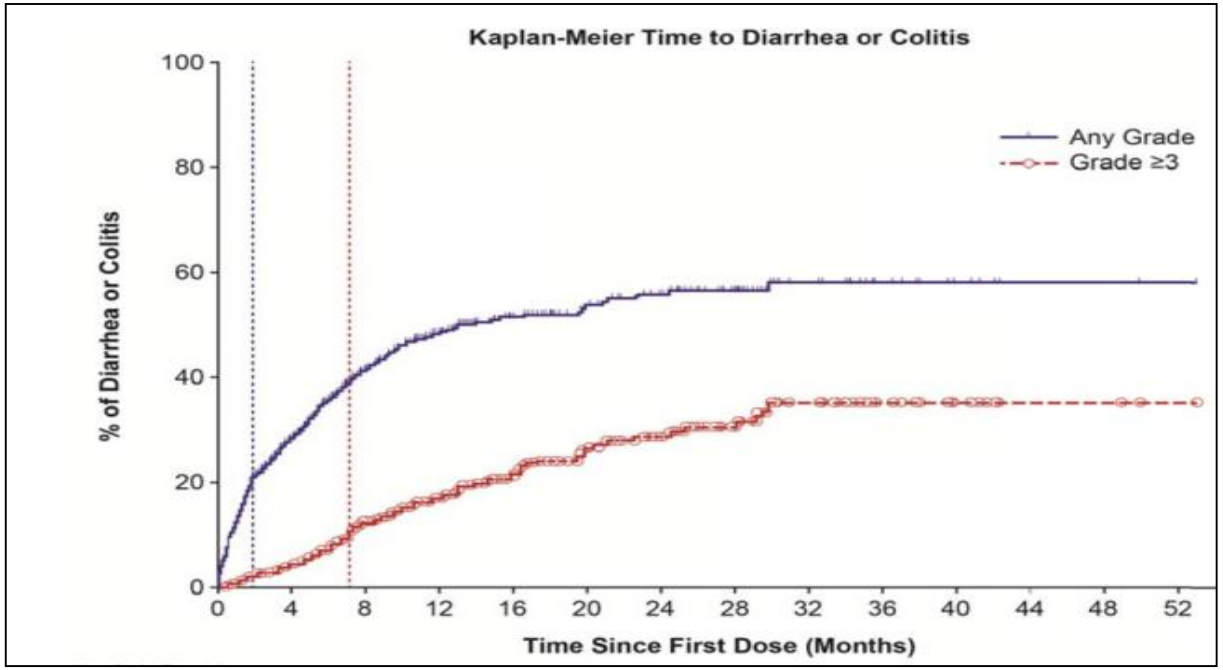
Inactivation of PI(3)K p110δ breaks regulatory T-cell-mediated immune tolerance to cancer

Khaled Ali[1]†, Dalya R. Soond[2]*†, Roberto Piñeiro[1]*, Thorsten Hagemann[3], Wayne Pearce[1], Ee Lyn Lim[2], Hicham Bouabe[2], Cheryl L. Scudamore[4], Timothy Hancox[5], Heather Maecker[6], Lori Friedman[6], Martin Turner[2], Klaus Okkenhaug[2]§ & Bart Vanhaesebroeck[1]§

Nature 2014:509:407

in CLL: PI3Kδ inhibition often leads to colitis

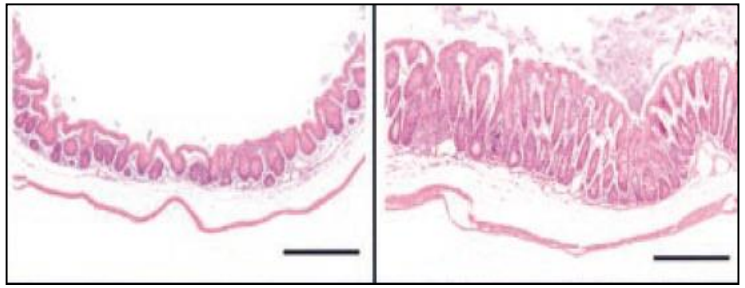
patients on PI3Kδ inhibitor:



diarrhoea & colitis

PI3Kδ-deficient mice:

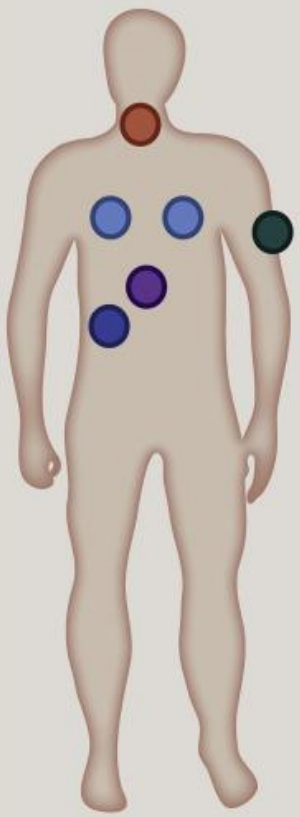
Class IA phosphoinositide 3-kinases (PI3Ks) are a family of p85/p110 heterodimeric lipid kinases that generate second messenger signals downstream of tyrosine kinases, thereby controlling cell metabolism, growth, proliferation, differentiation, motility, and survival. Mammals express three class IA catalytic subunits: p110α, p110β, and p110δ. It is unclear to what extent these p110 isoforms have overlapping or distinct biological roles. Mice expressing a catalytically inactive form of p110δ ($p110\delta^{D910A}$) were generated by gene targeting. Antigen receptor signaling in B and T cells was impaired and immune responses in vivo were attenuated in p110δ mutant mice. They also developed inflammatory bowel disease. These results reveal a selective role for p110δ in immunity.



wild-type PI3Kδ kinase-dead

Spectrum of adverse effects associated with PI3Kδ-inhibitors in B-cell malignancies is similar to that observed with anti-PD1/PDL1 & anti-CTLA4

Spectrum of adverse effects associated with PI3Kδ-inhibitors in B-cell malignancies is similar to that observed with anti-PD1/PDL1 & anti-CTLA4



Endocrinopathies: hypophysitis, hypothyroidism, hyperthyroidism		
	All grade	Grade 3+ events
Ipilimumab	10.9%	2.3%
Nivolumab	14.4%	0.6%
Ipilimumab and Nivolumab	30.0%	4.8%

Pneumonitis		
	All grade	Grade 3+ events
Ipilimumab	1.6%	0.3%
Nivolumab	1.3%	0.3%
Ipilimumab and Nivolumab	6.4%	1.0%

Gastrointestinal: colitis/diarrhea		
	All grade	Grade 3+ events
Ipilimumab	36.7%	11.6%
Nivolumab	19.5%	2.2%
Ipilimumab and Nivolumab	46.3%	14.7%

Skin toxicity: pruritis/rash/vitiligo		
	All grade	Grade 3+ events
Ipilimumab	54.0%	2.9%
Nivolumab	41.9%	1.6%
Ipilimumab and Nivolumab	59.1%	5.8%

Hepatic: increase AST and/or ALT		
	All grade	Grade 3+ events
Ipilimumab	7.1%	1.6%
Nivolumab	6.4%	2.6%
Ipilimumab and Nivolumab	30.0%	18.8%

Any select adverse event		
	All grade	Grade 3+ events
Ipilimumab	73.6%	18.6%
Nivolumab	62.0%	7.7%
Ipilimumab and Nivolumab	87.9%	39.6%

Callahan *et al*. *Immunity* 2016 **44:**1069–1078

Grade 3+ AEs with idelalisib PI3Kδ inhibitor	N=760
Pneumonitis	3%
Colitis/Diarrhoea	14%
Skin rash	6%
Hepatic inflammation/ ↑ALT/AST	14%

1. Coutre SE, *et al. Leuk Lymphoma* 2015; 56:2779–2786.
2. Coutre SE, *et al.* EHA 2015 (Abstract S433; oral).

Indolent Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia
clinicaloptions.com/oncology

CLINICAL CARE OPTIONS ONCOLOGY

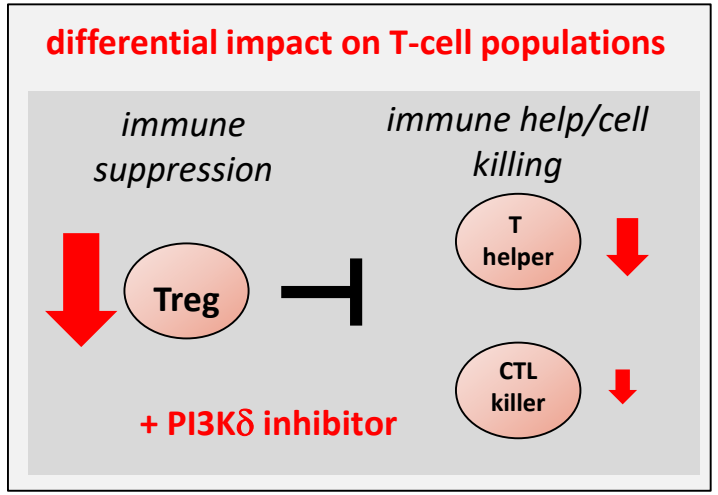
Idelalisib Label Black Box Warning

- Fatal and/or serious hepatotoxicity occurred in 14% of pts in clinical trials
  - Hepatic function should be monitored before and during treatment
  - Dose adjustments/discontinuation should be considered when necessary
- Fatal and/or serious and severe diarrhea or colitis occurred in 14% of pts in clinical trials
  - Pts should be monitored for these symptoms and dose adjustments or discontinuation should be considered when necessary
- Fatal and serious pneumonitis and intestinal perforation can occur during treatment
  - Dose adjustments or discontinuation should be considered when necessary

Idelalisib [package insert].

Can PI3Kδ and PI3Kγ inhibitors be used in solid tumours therapy?

PI3Kδ



+ PI3Kγ

macrophage re-polarisation towards anti-tumour

PI3Kγ is a molecular switch that controls immune suppression

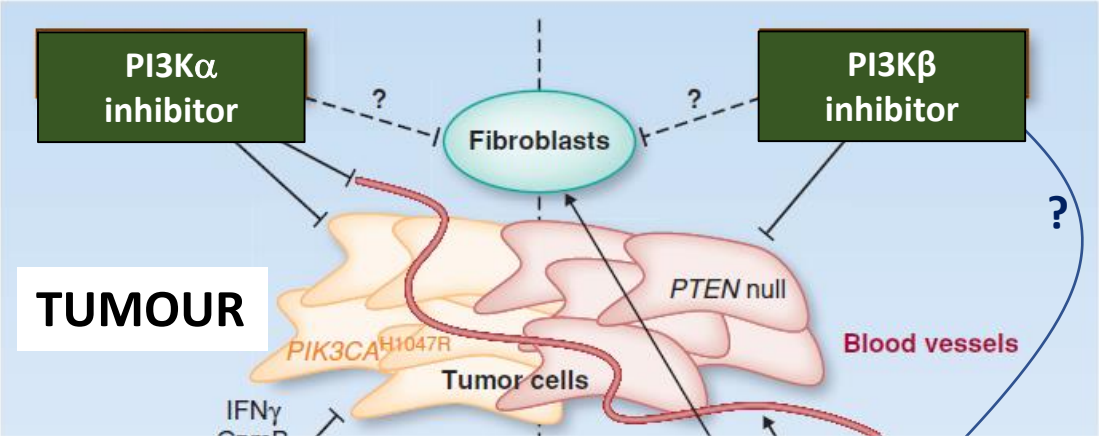
Megan M. Kaneda[1], Karen S. Messer[1,2], Natacha Ralainirina[1], Hongying Li[1,2], Christopher J. Leem[1], Sara Gorjestani[1], Gyunghwi Woo[1], Abraham V. Nguyen[1], Camila C. Figueiredo[1,3], Philippe Foubert[1], Michael C. Schmid[1], Melissa Pink[4], David G. Winkler[4], Matthew Rausch[4], Vito J. Palombella[4], Jeffery Kutok[4], Karen McGovern[4], Kelly A. Frazer[5,6], Xuefeng Wu[7], Michael Karin[7], Roman Sasik[8], Ezra E. W. Cohen[1,9] & Judith A. Varner[1,9,10]

Overcoming resistance to checkpoint blockade therapy by targeting PI3Kγ in myeloid cells

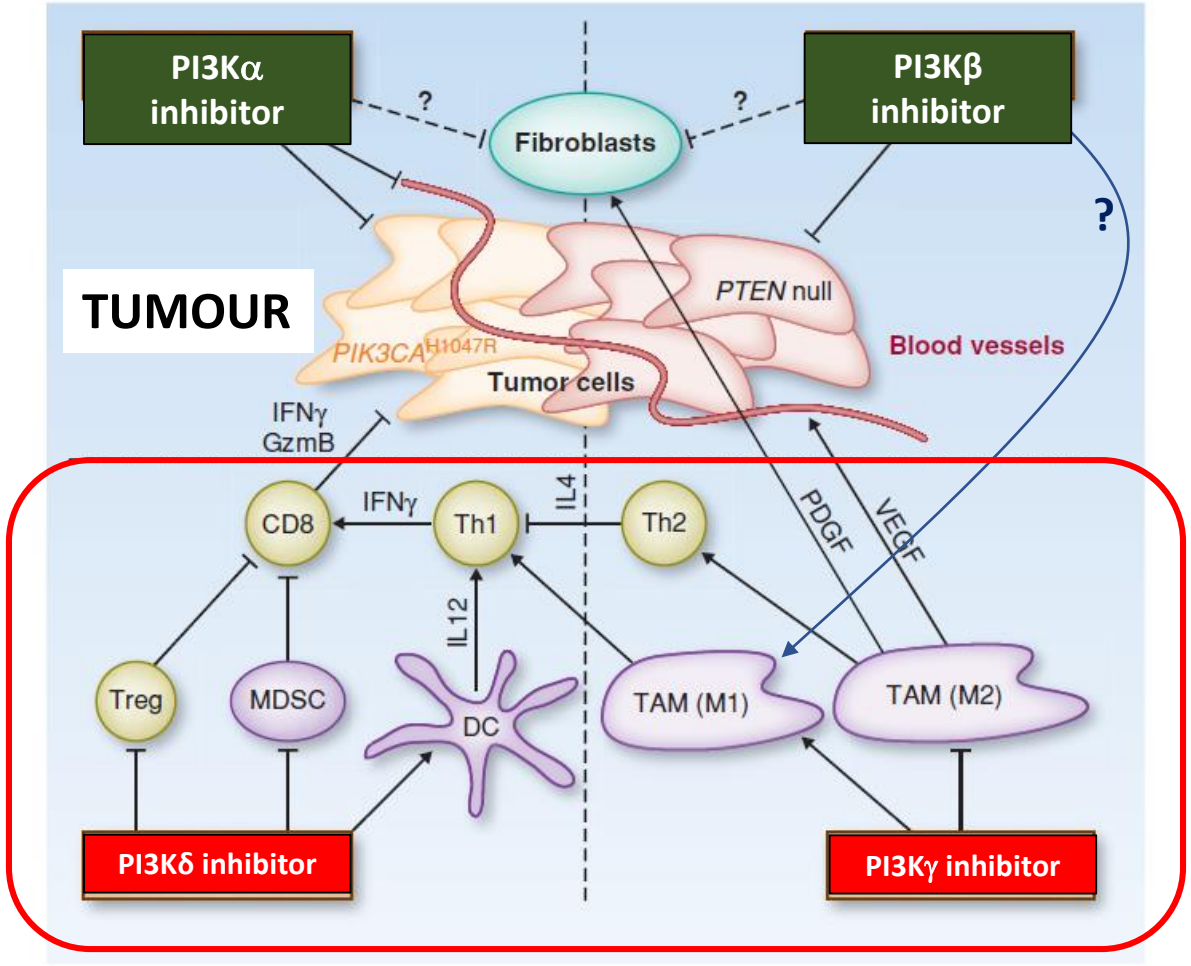
Olivier De Henau[1], Matthew Rausch[2], David Winkler[2], Luis Felipe Campesato[1], Cailian Liu[1], Daniel Hirschhorn-Cymerman[1], Sadna Budhu[1], Arnab Ghosh[1], Melissa Pink[2], Jeremy Tchaicha[2], Mark Douglas[2], Thomas Tibbitts[2], Sujata Sharma[2], Jennifer Proctor[2], Nicole Kosmider[2], Kerry White[2], Howard Stern[2], John Soglia[2], Julian Adams[2], Vito J. Palombella[2], Karen McGovern[2], Jeffery L. Kutok[2], Jedd D. Wolchok[1,3]§ & Taha Merghoub[1]§

Nature Nov 2016

The changing landscape of PI3K inhibition in cancer:



The changing landscape of PI3K inhibition in cancer:



Cancer immunotherapy using PI3K inhibitors?

can lymphoma-drug be used in solid tumours?

Okkenhaug K, Graupera M, Vanhaesebroeck B - *Cancer Discovery* 2016:6:1090

Ongoing clinical trials with PI3Kδ and γ inhibitors in solid tumours

Sponsor	Phase	Trial identifier	Inhibitor	Cancer type(s)	Combination
PI3Kδ					
CRUK and AMGEN	II	NCT02540928	AMG-319	Head and neck squamous cell carcinoma (nonviral)	None (no prior treatment)
TG Therapeutics	I	NCT02574663	TGR-1202	Various solid cancers	Chemotherapy
Incyte	I	NCT02646748	INCB050465	Various solid cancers	Pembrolizumab (anti-PD1)
Incyte	Ib	NCT02559492	INCB050465	Various solid cancers	INCB039110 (JAK1 inhibitor)
PI3Kγ					
Infinity	I/Ib	NCT02637531	IPI-549	Non-small cell lung cancer, melanoma	Pembrolizumab (anti-PD1)

→ ASCO 2018

→ AACR 2018

Okkenhaug K, Graupera M, Vanhaesebroeck B - *Cancer Discovery* 2016:6:1090

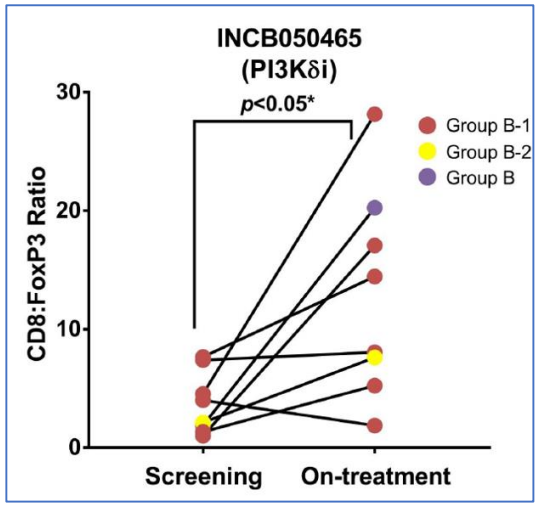
some early evidence for anti-tumour activity

BUT

PI3Kδ inhibitors are not without their *(on target)* problems

Incyte

Effect of JAK/STAT or PI3Kδ plus PD-1 inhibition on the tumor micro-environment: Biomarker results from a phase Ib study in patients with advanced solid tumors JM Kirkwood - AACR Presentation Chicago 2018



- ↓ intratumoral Tregs
- ↑ intratumoral $CD8^+$/Treg ratio
- ↑ markers of T-cell activation
- altered proteins involved in lymphocyte proliferation & IFNγ signalling in peripheral blood

INCB050465 (PI3Kδi) + pembrolizumab
- Relapsed SCLC: 2/4 responses (both PR; 2/3 responses in ICI naive)
- Relapsed NSCLC: 3/14 responses (1 CR; 3/10 responses in ICI naive)
- Relapsed urothelial carcinoma: 2/5 responses (2 CR; 2/3 responses in ICI naive)
- Relapsed melanoma: 1 CR in ICI refractory

https://investor.incyte.com/events-and-presentations/presentations

CRUK + AMGEN (lead: Christian Ottensmeier – Southampton)

AIM: quantify immunological effects of AMG319 on tumour microenvironment in HNSCC patients

- neo-adjuvant window study in non-pre-treated, operable HNSCC
- drug given for **20-29 days**, given before surgery
- blinded - 54 patients - randomised 2:1 AMG319/placebo
- trial currently on hold – analysis of immune markers pending

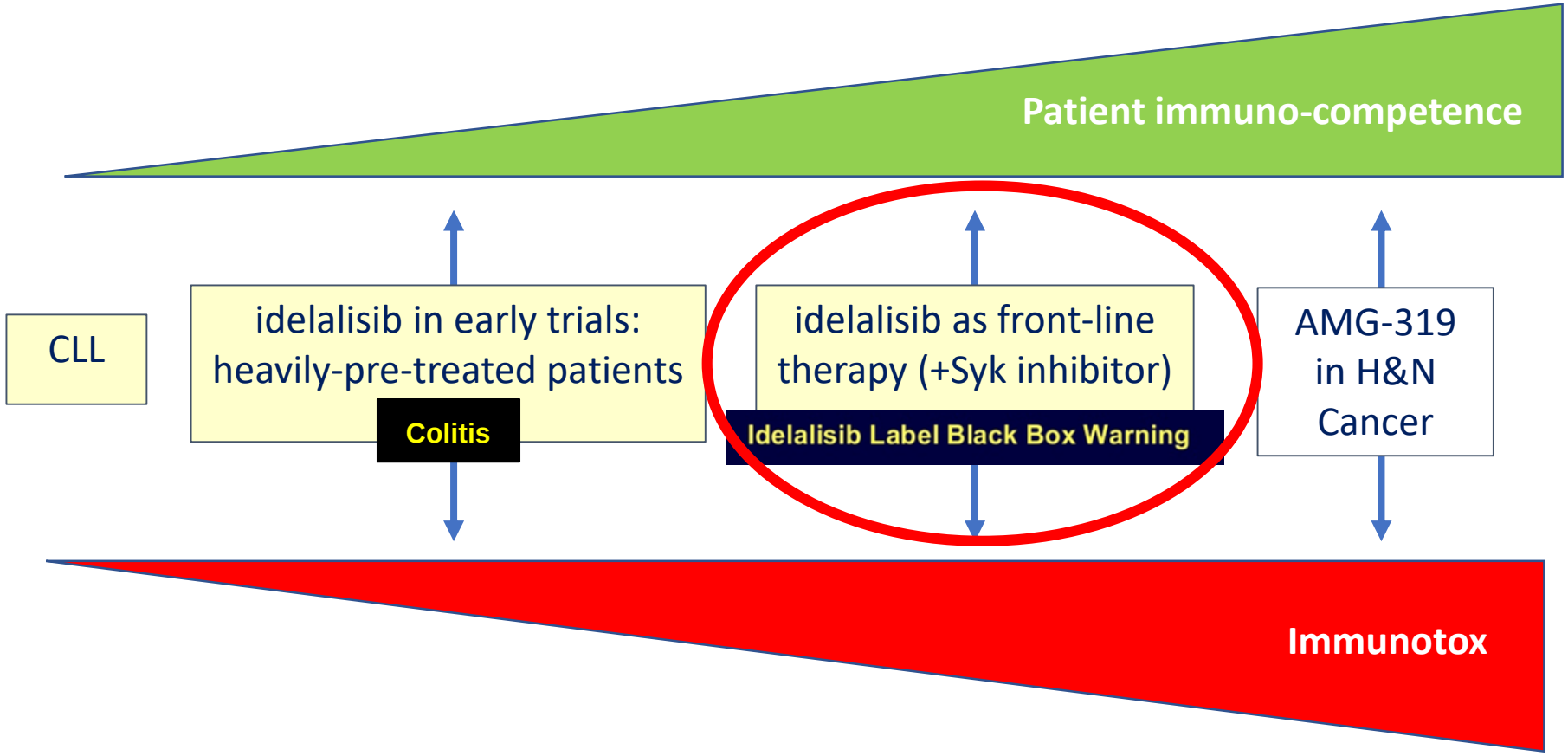
- 30 patients were given AMG319:
  - 10 patients: grade 2/3 treatment-related adverse events: rash, diarrhoea/colitis, vomiting, fever, flu-like symptoms - **toxicity presented from days 8-11**
  - 12 patients: early discontinuation due to adverse effects
  - adverse events resolved with withdrawal of drug and supportive treatment

Efficacy:

- 1 patient with T1 oral cavity carcinoma: pathological complete response
- other responses *(to be reviewed)*:
  - 2 patients: immune-related partial response
  - 16 patients: immune-related stable disease
  - 6 patients: immune-related progressive disease

http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.6068

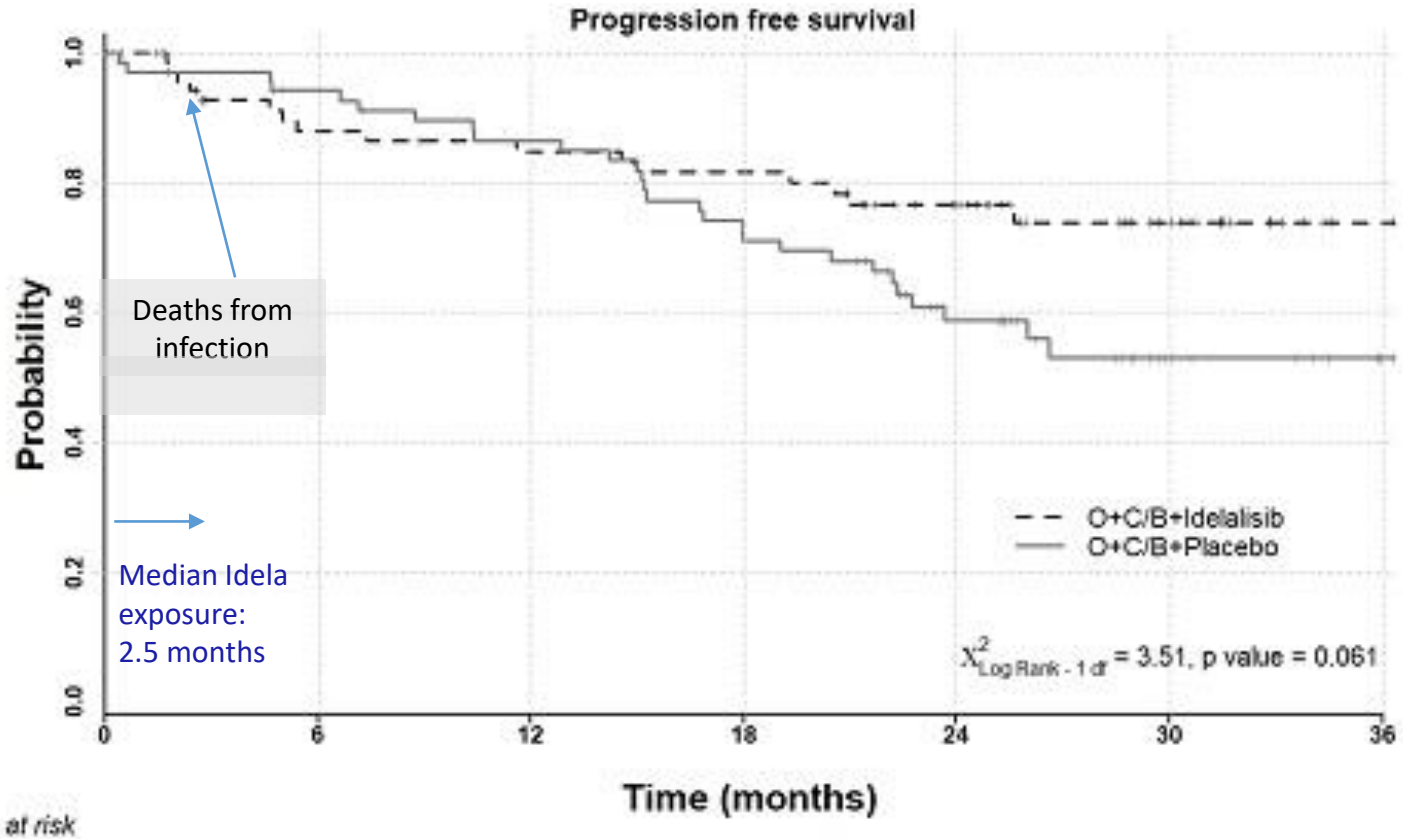
Immuno-competence as a key factor in PI3Kδ-inhibitor tox?



EFFECT OF ADDING IDELALISIB TO FRONTLINE OFATUMUMAB PLUS EITHER CHLORAMBUCIL OR BENDAMUSTINE IN LESS FIT PATIENTS WITH CLL: UPDATED RESULTS FROM THE NCRI RIALTO TRIAL.

Author(s): Andrew Pettitt, Nagesh Kalakonda, Fotis Polydoros, Matthew Bickerstaff, Geetha Menon, Sarah Coupland, Melanie Oates, Ke Lin, Christopher Pocock, Stephen Jenkins, Anna Schuh, Farooq Wandroo, Saad Rassam, Andrew Duncombe, Paul Cervi, Shankara Paneesha, Maadh Aldouri, Christopher Fox, Christopher Knechtli, Mike Hamblin, Deborah Turner, Peter Hillmen

EHA Learning Center. Pettitt A. Jun 15, 2018; 214820



Numbers at risk

O+C/B+Idelalisib	73	56	53	50	38	20	5
O+C/B+Placebo	72	62	56	46	28	11	3

Died from CLL progression:

Idelalisib: 0/73

Placebo: 10/72

Immuno-suppression/activation by PI3K-pathway modulation:

- not restricted to PI3Kδ? -

PI3Kδ/Akt inhibition:

potentiates *ex-vivo* cultured TILs and CAR-T cells: keeps cells less differentiated

immune cells:

PI3Kδ
↓
Akt
↓
mTOR

Inhibition of Akt signaling promotes the generation of superior tumor-reactive T cells for adoptive immunotherapy

Anniek B. van der Waart,[1] Noortje M. P. van de Weem,[1] Frans Maas,[1] Cynthia S. M. Kramer,[1] Michel G. D. Kester,[2] J. H. Frederik Falkenburg,[2] Nicolaas Schaap,[3] Joop H. Jansen,[1] Robbert van der Voort,[1] Luca Gattinoni,[4] Willemijn Hobo, and Harry Dolstra[1]

Blood 2014:124:3490

PI3Kδ Inhibition Enhances the Antitumor Fitness of Adoptively Transferred CD8+ T Cells

Jacob S. Bowers[1,2,3], Kinga Majchrzak[1,2,3,4], Michelle H. Nelson[1,2,3], Bulent Arman Aksoy[5], Megan M. Wyatt[1,2,3], Aubrey S. Smith[1,2,3], Stefanie R. Bailey[1,2,3], Lillian R. Neal[1,2,3], Jeffrey E. Hammerbacher[1,5] and Chrystal M. Paulos[1,2,3]**

Front. Immunol. 2017:8:1221

Akt Inhibition Enhances Expansion of Potent Tumor-Specific Lymphocytes with Memory Cell Characteristics

Joseph G. Crompton[1,2,3], Madhusudhanan Sukumar[1], Rahul Roychoudhuri[1], David Clever[1,3], Alena Gros[1], Robert L. Eil[1], Eric Tran[1], Ken-ichi Hanada[1], Zhiya Yu[1], Douglas C. Palmer[1], Sid P. Kerkar[1], Ryan D. Michalek[4], Trevor Upham[1], Anthony Leonardi[1], Nicolas Acquavella[1], Ena Wang[5], Francesco M. Marincola[5], Luca Gattinoni[1], Pawel Muranski[1], Mark S. Sundrud[6], Christopher A. Klebanoff[1,7], Steven A. Rosenberg[1], Douglas T. Fearon[3], and Nicholas P. Restifo[1]

Cancer Res. 2015:75: 2015:296

Inhibition of AKT signaling uncouples T cell differentiation from expansion for receptor-engineered adoptive immunotherapy

Christopher A. Klebanoff,[1,2,3] Joseph G. Crompton,[3,4] Anthony J. Leonardi,[3] Tori N. Yamamoto,[3,5] Smita S. Chandran,[1,2] Robert L. Eil,[3] Madhusudhanan Sukumar,[3] Suman K. Vodnala,[3] Jinhui Hu,[3,6] Yun Ji,[3,6] David Clever,[3] Mary A. Black,[3] Devikala Gurusamy,[3] Michael J. Kruhlak,[7] Ping Jin,[8] David F. Stroncek,[8] Luca Gattinoni,[3,6] Steven A. Feldman,[3] and Nicholas P. Restifo[3,9]

JCI Insight 2017:2:e95103

Improving T-cell expansion and function for adoptive T-cell therapy using ex vivo treatment with PI3Kδ inhibitors and VIP antagonists

Christopher T. Petersen,[1] Mojibade Hassan,[1] Anna B. Morris,[1] Jasmin Jeffery,[1,2] Kunhee Lee,[1] Neera Jagirdar,[1] Ashley D. Staton,[1] Sunil S. Raikar,[3] Harold T. Spencer,[3] Todd Sulchek,[4] Christopher R. Flowers,[1] and Edmund K. Waller[1]

Blood Adv. 2018:2:210

NCT03139370: first clinical trial to incorporate Akt-inhibitor in T-cell manufacturing process

Immuno-suppression/activation by PI3K-pathway modulation:

- not restricted to PI3Kδ? -

immune cells:

PI3Kδ
↓
Akt
↓
mTOR

TORC1 inhibition enhances immune function and reduces infections in the elderly

Joan B. Mannick[1]*†, Melody Morris[1], Hans-Ulrich P. Hockey[2], Guglielmo Roma[3], Martin Beibel[3], Kenneth Kulmatycki[1], Mollie Watkins[1], Tea Shavlakadze[1], Weihua Zhou[1], Dean Quinn[4], David J. Glass[1], Lloyd B. Klickstein[1]*

Science Transl Med 2018 Jul 11;10(449). pii: eaaq1564

NEWS&**ANALYSIS**

INFECTIOUS DISEASE

Immune Suppressant Unexpectedly Boosts Flu Vaccine

Science 2013:342:413

SUMMARY

many challenges remain for PI3K-pathway-based therapy to be effective in cancer:

1. currently clinically-impactful PI3K inhibitors mainly act through non-cytotoxic mechanisms ?

SUMMARY

many challenges remain for PI3K-pathway-based therapy to be effective in cancer:

1. **currently clinically-impactful PI3K inhibitors mainly act through non-cytotoxic mechanisms ?**

I. interference with cancer-type-specific biology:

→ breast cancer (PI3Kα):

- making hormone therapy work (better)

→ B-cell leukaemia (PI3Kα, PI3Kδ):

- interfering with leukaemia-specific biology (pro-survival/homing/adhesion signals) (PI3Kδ)
- blocking supportive stromal cells (PI3Kδ)
- blocking crosstalk between leukaemic cells and stroma (PI3Kδ)

SUMMARY

many challenges remain for PI3K-pathway-based therapy to be effective in cancer:

1. **currently clinically-impactful PI3K inhibitors mainly act through non-cytotoxic mechanisms ?**

I. interference with cancer-type-specific biology:

→ breast cancer (PI3Kα):

- making hormone therapy work (better)

→ B-cell leukaemia (PI3Kα, PI3Kδ):

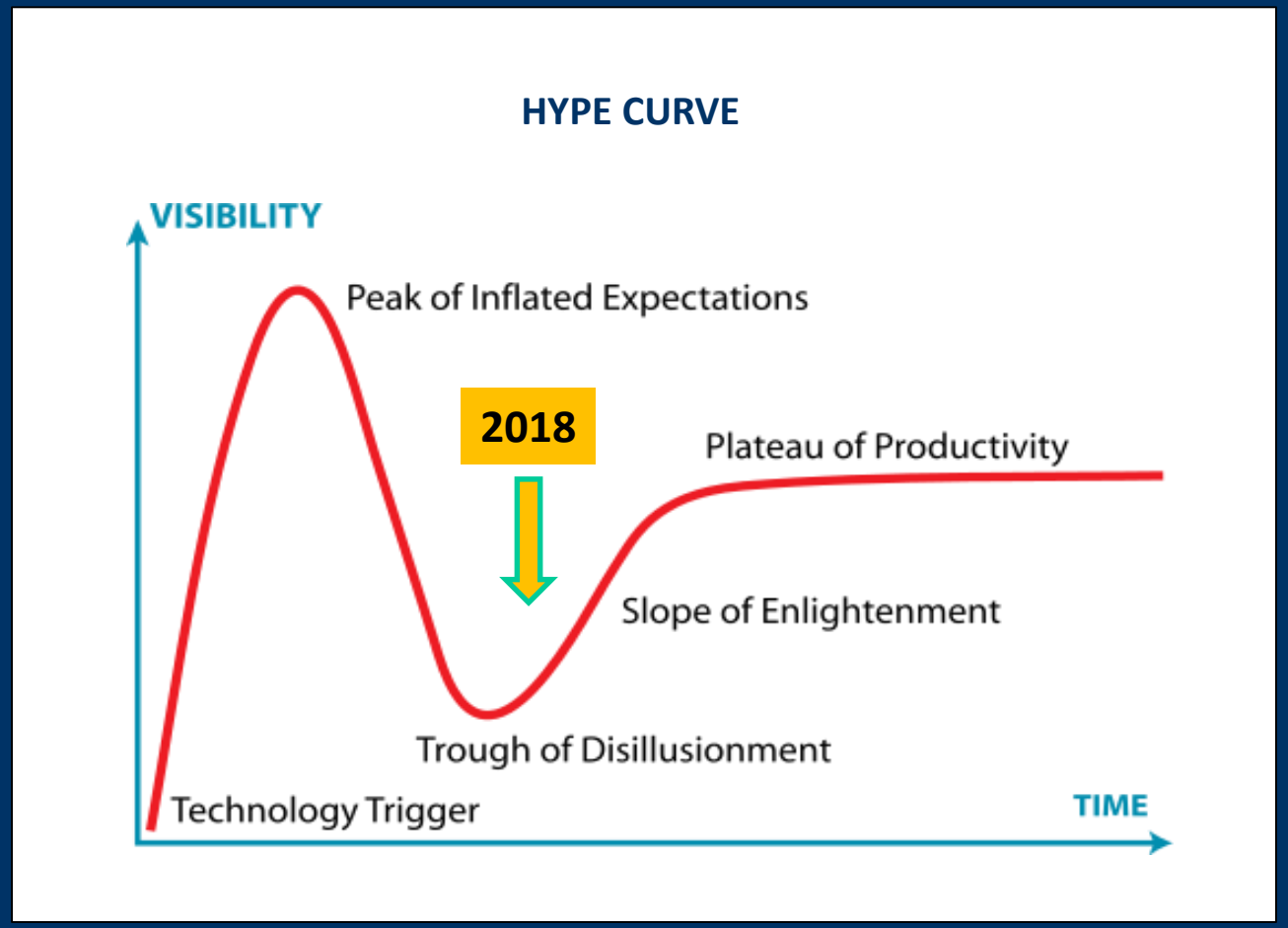
- interfering with leukaemia-specific biology (pro-survival/homing/adhesion signals) (PI3Kδ)
- blocking supportive stromal cells (PI3Kδ)
- blocking crosstalk between leukaemic cells and stroma (PI3Kδ)

II. stimulation of a host anti-tumour immune response (PI3Kδ, PI3Kγ)

2. go PI3K isoform-selective!

SUMMARY

many challenges remain for PI3K-pathway-based therapy to be effective in cancer:



Acknowledgements

UCL Cancer Institute

Khaled Ali

Roberto Piñeiro

Wayne Pearce

Genentech

Lori Friedman *et al.*

Babraham – Cambridge - UK

Klaus Okkenhaug

Dalya Soond

Lyn Lim

Hicham Bouabe

Southampton CRUK

Christian Ottensmeier *et al.*

CRUK

Centre for Drug

Development Team

Amgen

Christian Rommel *(now Roche)*

Gregory Friberg *et al.*

Acknowledgements

CANCER RESEARCH UK

BBSRC bioscience for the future

LUDWIG INSTITUTE FOR CANCER RESEARCH

MRC Medical Research Council

UCL Hospitals Biomedical Research Centre
A partnership between UCL and University College London Hospitals NHS Foundation Trust

Acknowledgements

THANK YOU!

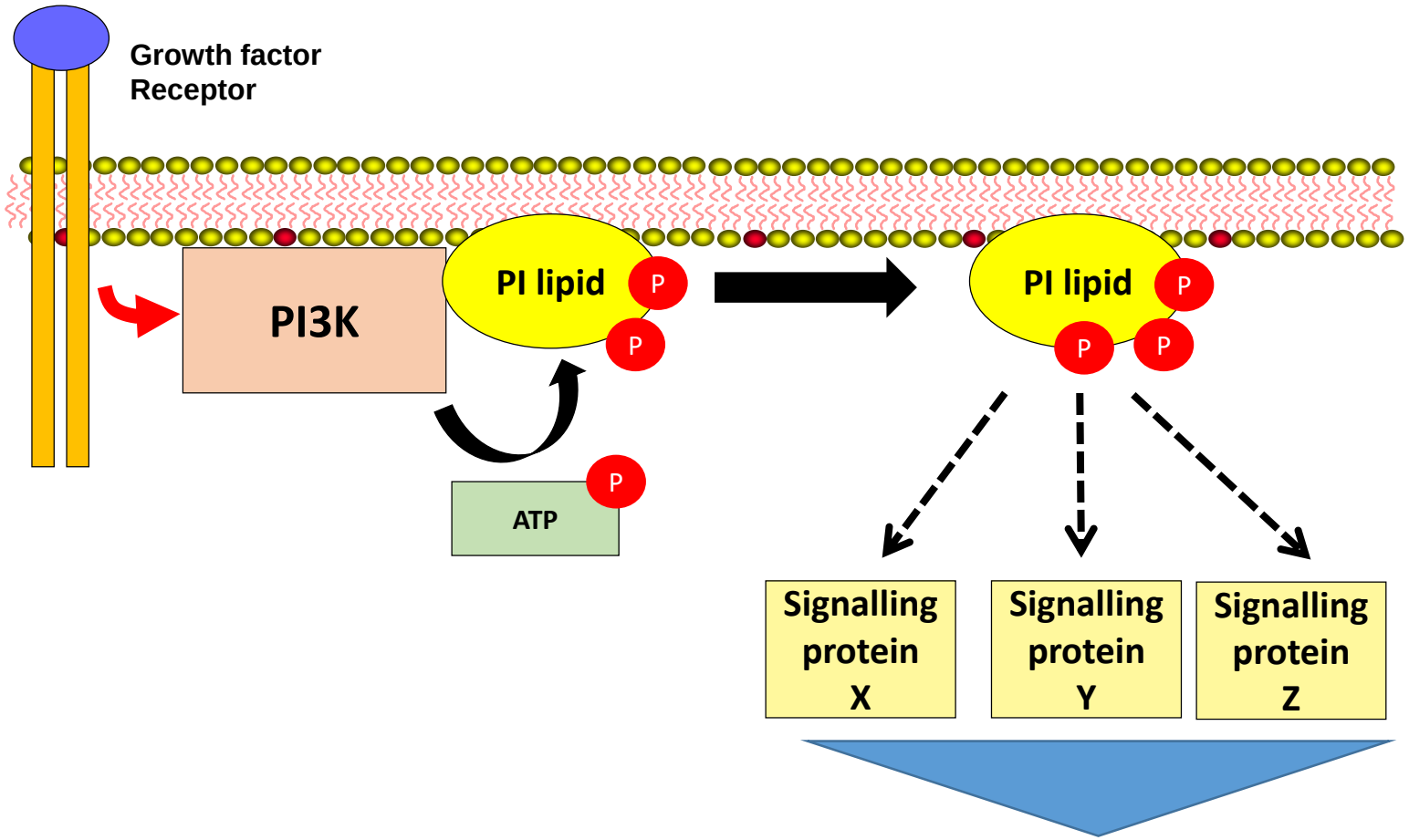
SUMMARY

anti-cancer effect of PI3Kδ-inhibitors	haem-onc	solid tumours
direct	yes, but not directly cytotoxic, rather: interference with antigen receptor signalling & interactions with stroma	↑ PI3Kδ expression upon breast cancer progression? *(e.g. Cell Death and Disease* 2018:9:678)
stromal	• ↓ stromal support cells • ↑ adaptive immune response	• ↓ cancer inflammation • ↑ adaptive immune response

PI3Kδ inhibition = small molecule approach to break immune tolerance in cancer

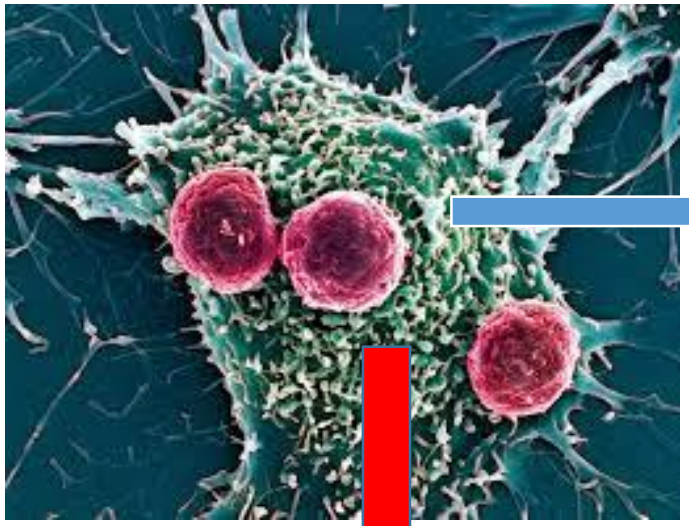
PI 3-kinase (PI3K) in cell signalling

MERGE the next 3 slides



cell cycle progression – migration – proliferation - …

PI3K inhibition in cancer may need a re-think

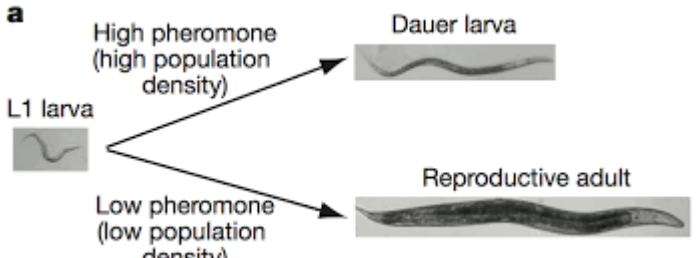


targeting PI3K in the cancer cell : CHALLENGING

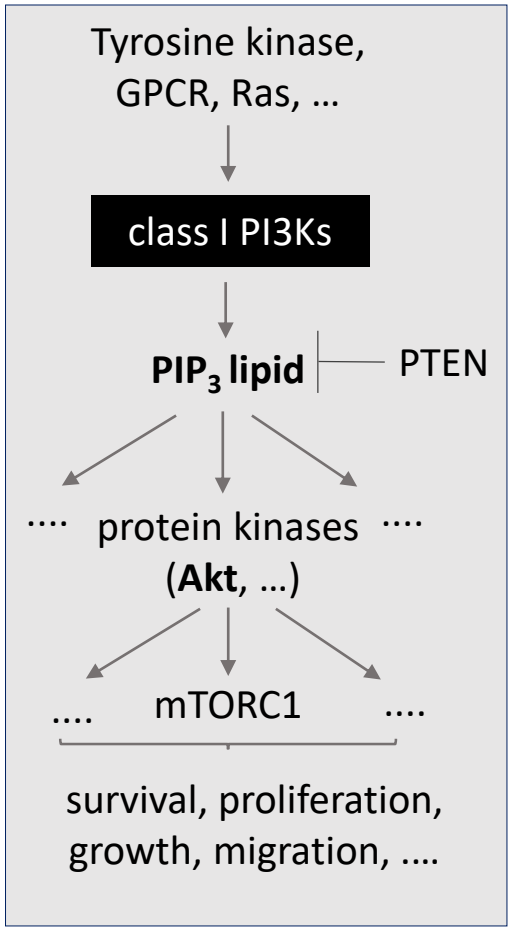
key question: what to expect from PI3K inhibition?

→ not cell death – cytostasis at best?
→ make other therapies work better?
eg. hormone therapy in breast cancer

targeting PI3K in immune cells: cancer immunotherapy?



Class I PI3K isoforms as drug targets in cancer



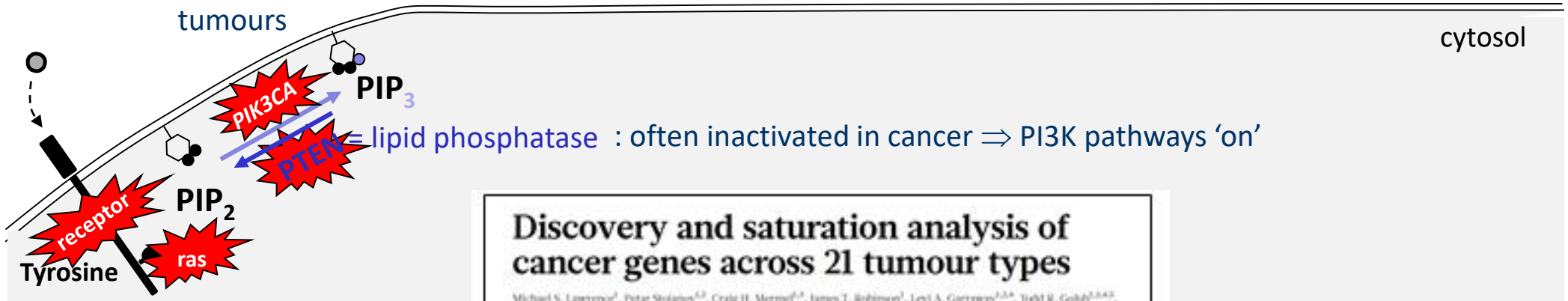
TALK:

1. role of *PIK3CA* mutation in cancer

2. update on PI3Kδ-based anti-cancer therapy

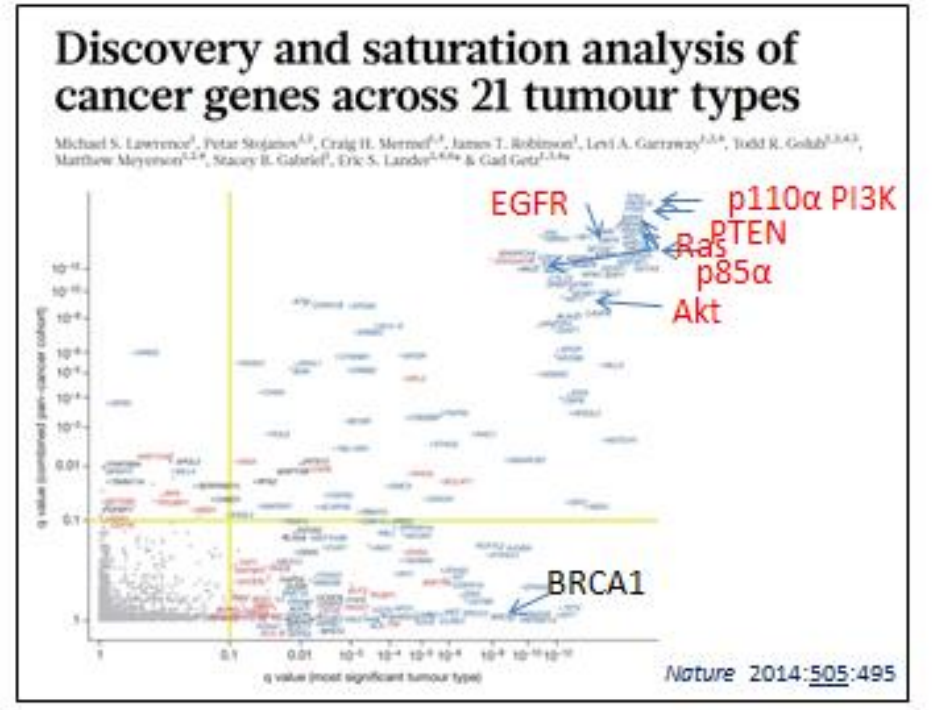
Class I PI3K signalling in cancer

PIK3CA mutations are very frequent in solid tumours



≡ lipid phosphatase : often inactivated in cancer ⇒ PI3K pathways 'on'

Tyrosine kinases, GPCRs, small GTPases



The PI3K pathway has been implicated in RESISTANCE to various anti-cancer therapies

including chemotherapy – radiotherapy - hormone therapy - targeted agents

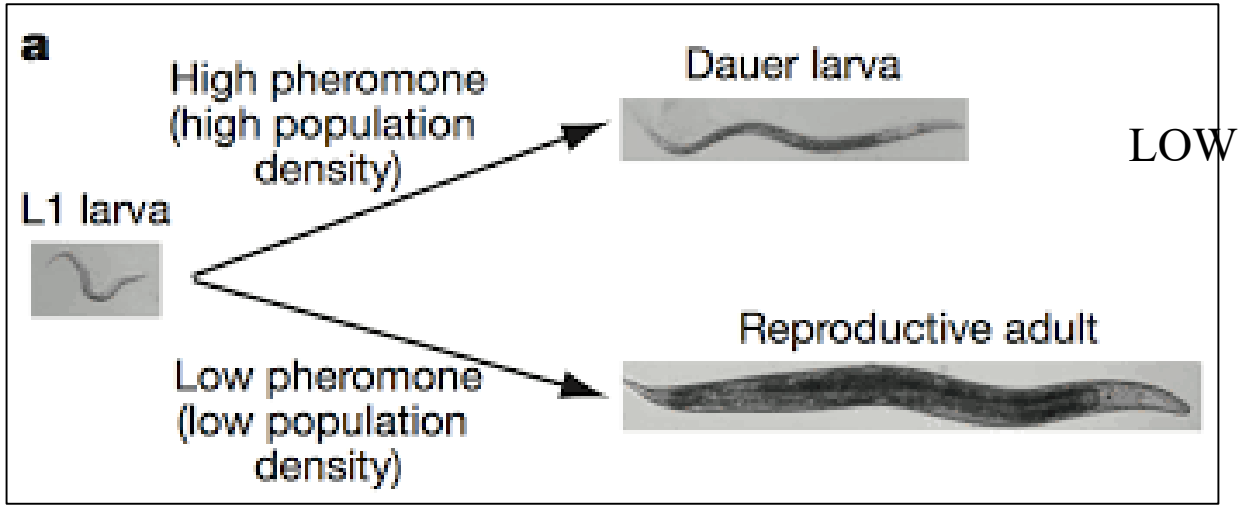
development of class I PI3K inhibitors for cancer therapy

targeting individual or groups of class I PI3Ks

thus far: modest impact in solid tumours

- if effect: mainly cytostatic

what can be expected of PI3K inhibition?



LOW PI3K

NORMAL PI3K

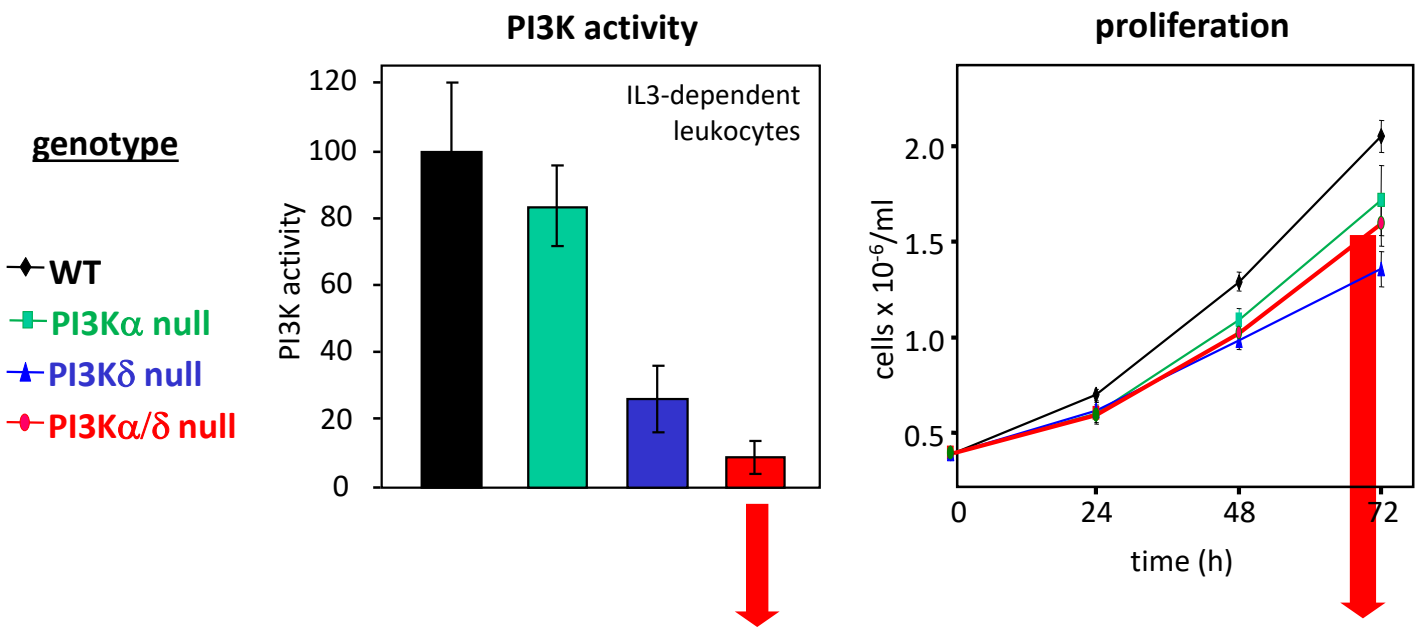
Cells can live with very little class I PI3K activity

Activity of any class IA PI3K isoform can sustain cell proliferation and survival

Lazaros C. Foukas[a,1,2], Inma M. Berenjeno[a], Alexander Gray[b], Asim Khwaja[c,3], and Bart Vanhaesebroeck[a,3]

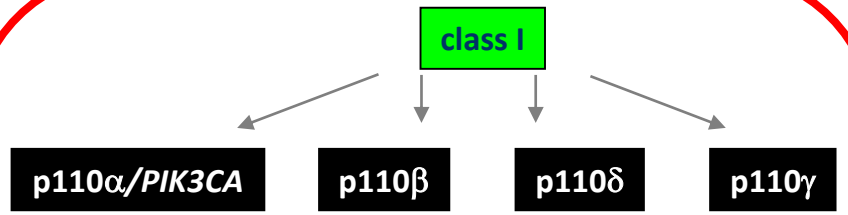
PNAS 2010:107:11381

intercross kinase-dead class I PI3K knock-in mice & derive stable cell lines

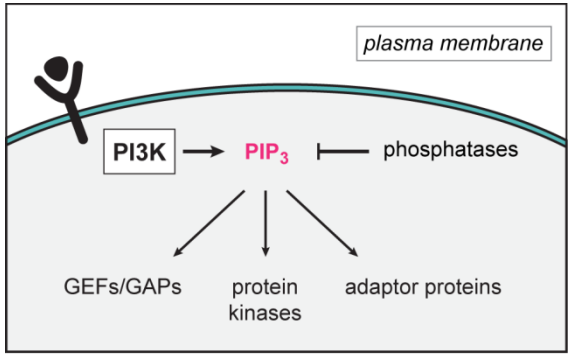


cells can survive/proliferate with <10% of their class IA PI3K activity (!)

PI 3-kinase – a family of enzymes

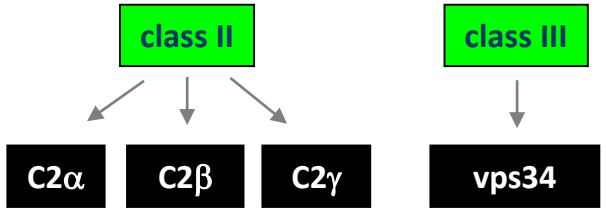


- act on the plasma membrane
- couple to cell surface signalling receptors

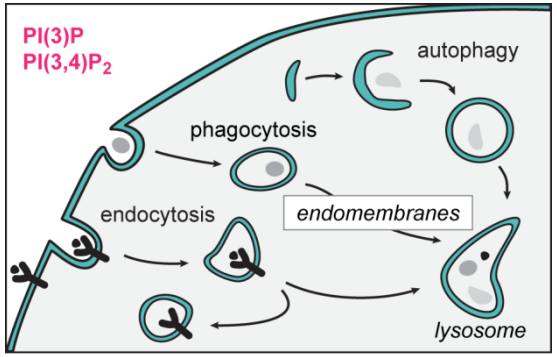


SIGNAL TRANSDUCTION

- implicated in cancer – metabolism – thrombosis - immunity/inflammation - …



- act on endo-membranes
- regulate intracellular vesicular traffic



VESICULAR TRAFFIC

- disease indications: ?

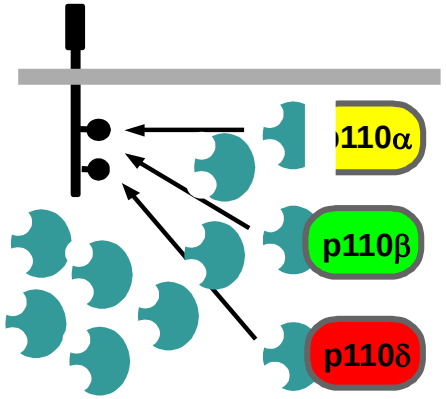
PI3K knock-out (KO) mice:

PI3K gene deletion/KO → often: - deregulation of PI3K subunit expression

- paradoxical results

p110α KO mice

(Bi *et al.* JBC 1999:274:10963)



in homozygous embryos:

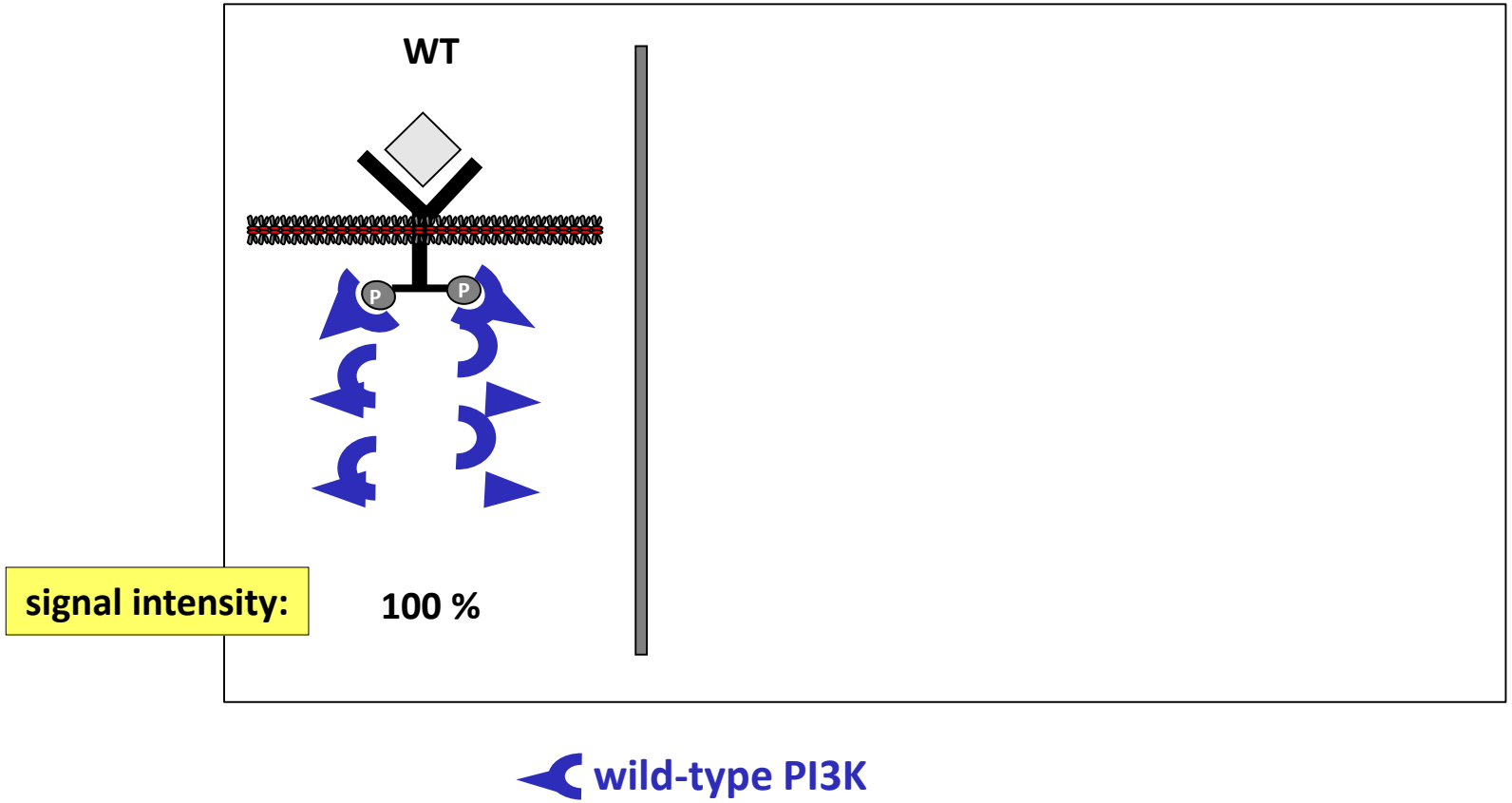
p85 adaptor overexpression

↓

dominant-negative for all p110 isoforms?

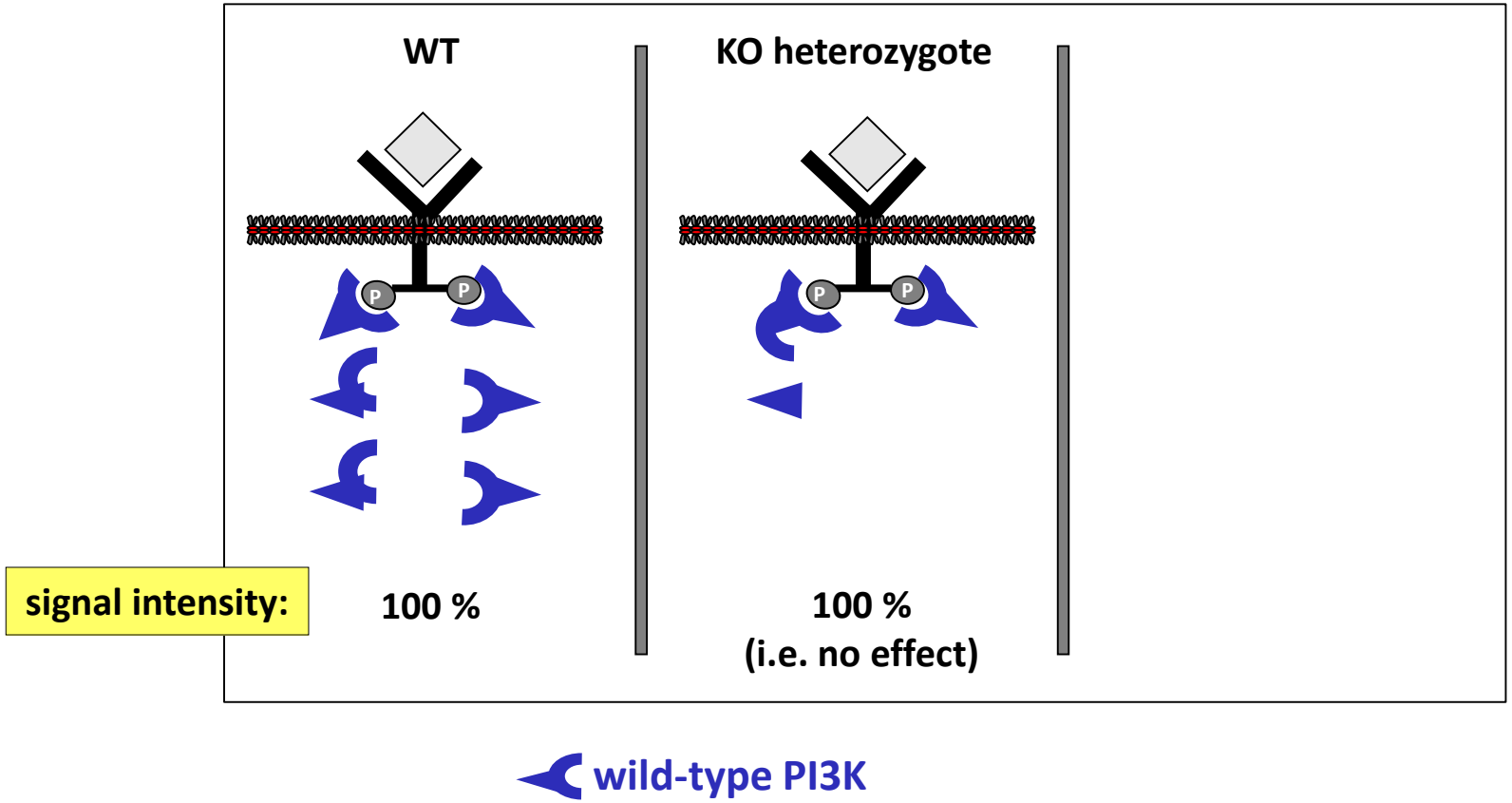
PI3K kinase-dead KI mice show phenotypes in heterozygous state

≈ drug action



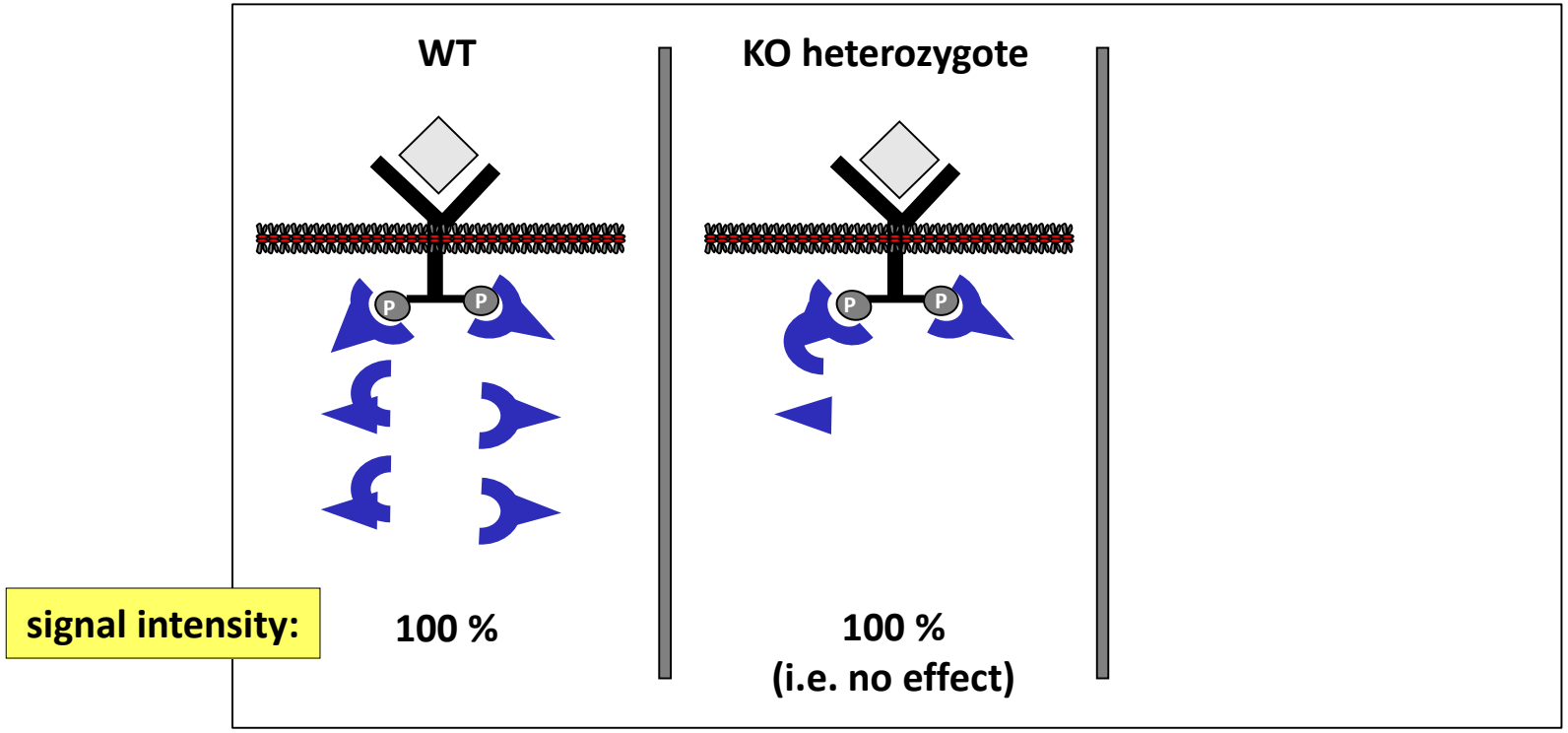
PI3K kinase-dead KI mice show phenotypes in heterozygous state

≈ drug action



PI3K kinase-dead KI mice show phenotypes in heterozygous state

≈ drug action

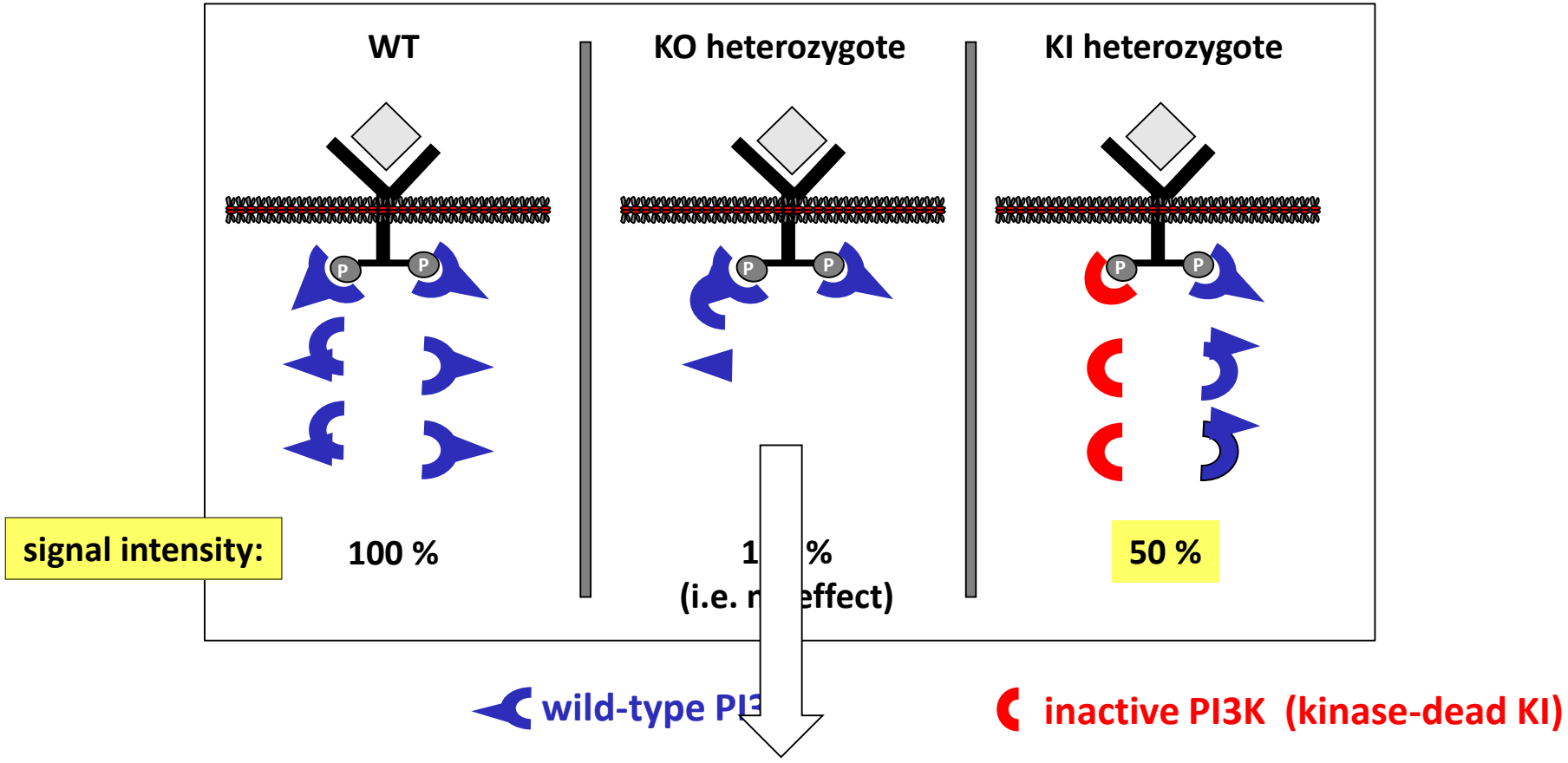


wild-type PI3K

inactive PI3K (kinase-dead KI)

PI3K kinase-dead KI mice show phenotypes in heterozygous state

≈ drug action



heterozygous KO expected to give phenotype ONLY when PI3K expression is limiting, relative to receptors

KO *versus* KI:
KO allows compensation by non-targeted isoforms – milder phenotypes