IMPAKT
BREAST CANCER CONFERENCE

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Translational research

# Clinical Perspectives and Debate: Xenograft models of solid tumours - Problems, pitfalls and future directions

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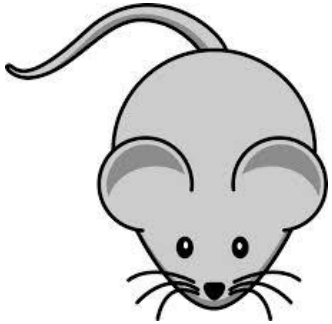
IMPAKT Breast Cancer Conference 2014

# Disclosure slide

- The Walter and Eliza Hall Institute has a commercial agreement with Abbvie (formerly Abbott) and Genentech and receives commercial income related to ABT-199.
- I have no personal financial interest and receive no grant funding from Abbvie or Genentech.

# Xenograft models of solid tumours: Problems, pitfalls and future directions



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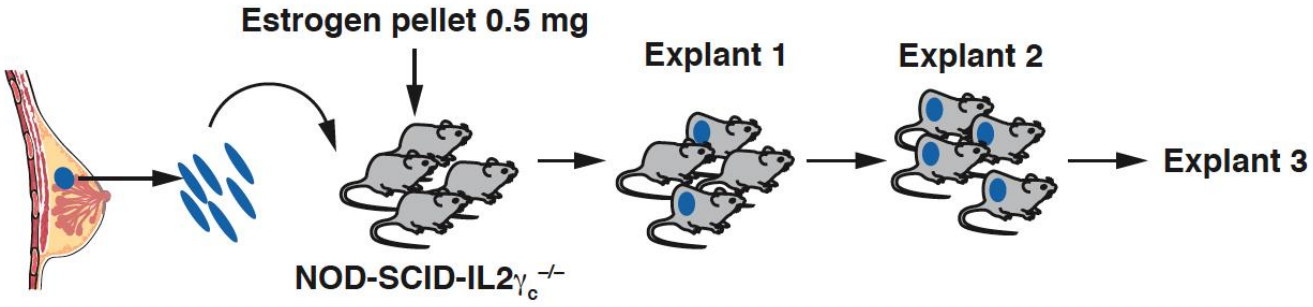
# Models to study tumour biology and potential therapeutic agents




| | |
|---|---|
| Cell Lines | Selected through multiple passages, acquisition of multiple mutations. (MCF-7 c.1970) |
| Animal Tumour Models | Genetic modification/ mutagenesis resulting in tumour predisposition.<br>Differences between species. |
| Cell line derived xenografts | Selected through multiple passages, acquisition of multiple mutations.<br>*Do not recapitulate tumour heterogeneity.*<br>*Rarely form metastases.* |
| Patient-Derived Xenografts<br>'PDX' models | *Often recapitulate tumour heterogeneity and behaviour; share genomic features with the primary tumour.*<br>*May form metastases.* |

# PDX models – problems and pitfalls

- Only a proportion of primary breast tumours engraft
  **TNC > HER2 > Luminal B** >> Luminal A tumours

- 'Take rate' likely depends on a variety of factors:
  - Immunodeficient model (NSG ≈ SCID-Beige > NOD-SCID > nude)
  - Source (primary vs metastasis)
  - Site (orthotopic/cleared mammary fat pad, sc fat)
  - Matrigel and stromal cells? (eg MSCs, fibroblasts)
  - Estradiol supplementation often required (helpful for $ER^-$ tumours?)

- Tumour latency generally measured **over months**, making 'real-time evaluation' for patients a challenge
  - *Ex vivo* tumour culture systems?

- Faithfully recapitulate the tumour genome but may undergo 'genetic drift' or **clonal evolution** on serial passaging

- Lack of immune system renders them
  - Highly susceptible to infection
  - NOD-SCID mice develop thymic lymphoma
  - **Compromises immunotherapy-based studies**

# Differential engraftment between been tumour subtypes

| Tumour Subtype | Take rate* | |
|---|---|---|
| **Triple negative / basal-like** | 17/28 | (60.7 %) |
| **Luminal** | | |
| $ER^+ PR^{+ \text{ or } -}$ | 13/108 | (12.0 %) |
| $ER^- PR^+$ | 2/8 | (25.0 %) |
| **HER2-positive** | 5/14 | (35.7 %) |
| Total | 37/158 | (23.4 %) |

Data for 2008 – 2011
* Tumours that engrafted and were capable of serial passage

François Vaillant

# PDX models – problems and pitfalls

- Only a proportion of primary breast tumours engraft
  **TNC > HER2 > Luminal B** >> Luminal A tumours

- '**Take rate**' likely depends on a variety of factors:
  - Immunodeficient model (NSG ≈ SCID-Beige > NOD-SCID > nude)
  - Source (primary versus metastasis)
  - Site (orthotopic/cleared mammary fat pad, sc fat)
  - Stroma, ECM, ligands (eg MSCs, fibroblasts/CAFs, Matrigel, prolactin)
  - Estradiol supplementation often required (helpful for $ER^-$ tumours?)

- **Tumour latency** generally measured **over months**, making real-time evaluation for patients a challenge
  - Develop predictive indicators? *Ex vivo* culture systems?

- Faithfully recapitulate the tumour genome but may undergo **'genetic drift'** or **clonal evolution** on serial passaging (can be tracked)

- Lack of immune system renders them
  - Highly susceptible to infection
  - NOD-SCID mice develop thymic lymphoma
  - **Compromises immunotherapy-based studies**

# PDX models – opportunities

**(1) Recapitulate tumour heterogeneity**

- A preferred model for *in vivo* cancer stem cell studies [Al Hajj et al *PNAS* 2003]
- Clonal representation is maintained on transplantation [Li et al, *Cell Rep* 2013]
- Luminal xenografts retain hormone receptor heterogeneity and endocrine responsiveness [Kabos et al *Breast Cancer Res Treat* 2012]

**(2) Amenable to 'discovery' research**

- Early passage (treatment-naïve) PDX models may select for the subset of cells prone to metastasis [Ding et al Nature 2010]
- Enable genomic studies that identify driver mutations (eg *ESR1* variants)
- Study metastasis [Marangoni et al *Clin Cancer Res* 2007; De Rose *Nature Med* 2011; Zhang et al *Cancer Res* 2013; Li et al, *Cell Rep* 2013]
- Lentiviral transduction, *in vivo* imaging and cell tracing, 'humanisation'

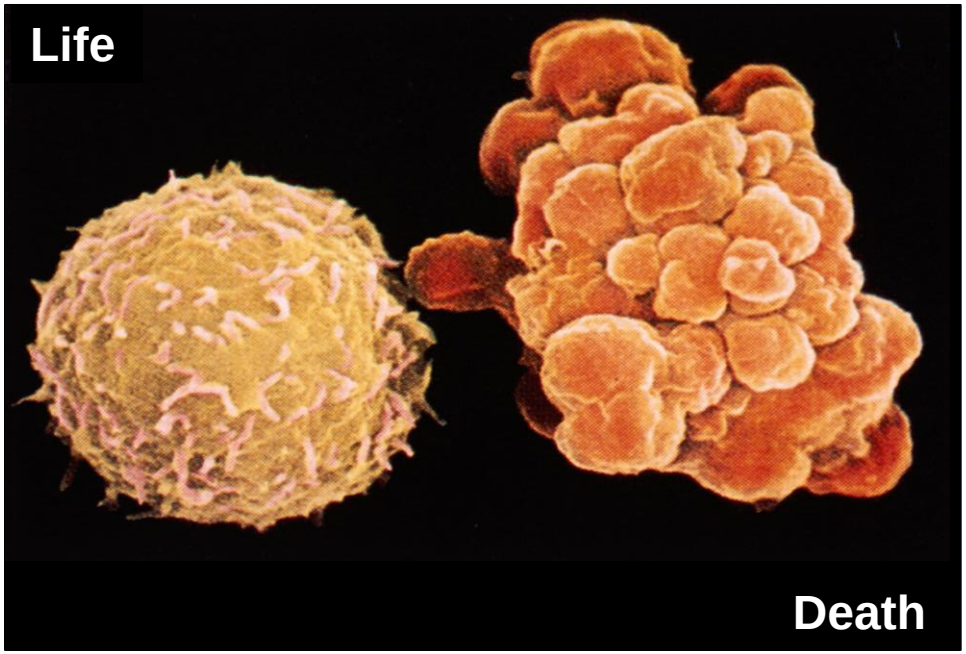
**(3) Renewable source of tumour**

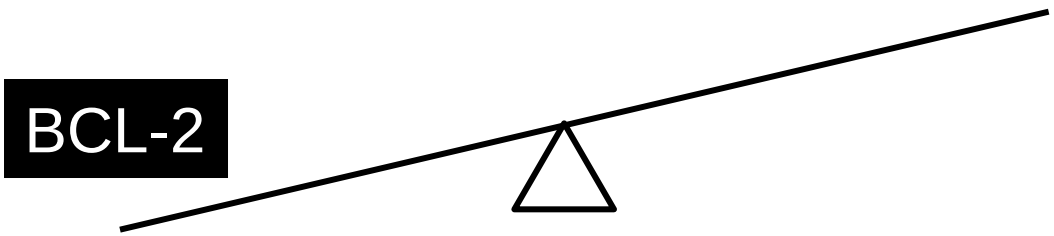
- Tumour sphere assays, Dissociated tumour cultures

**(4) Offer pre-clinical models for evaluation novel therapies (response/resistance)**

- DLL4 [Hoey et al *Cell Stem Cell* 2009], CXCR1 [Ginestier et al *JCI* 2010], Stat3 inhibitors [Dave et al *Plos One* 2012], Notch inhibitors [Schott et al *Clin Cancer Res* 2013], Estradiol [Li et al *Cell Rep*, 2013]
- BCL-2 inhibitors [Oakes et al *PNAS* 2012; Vaillant et al *Cancer Cell* 2013]

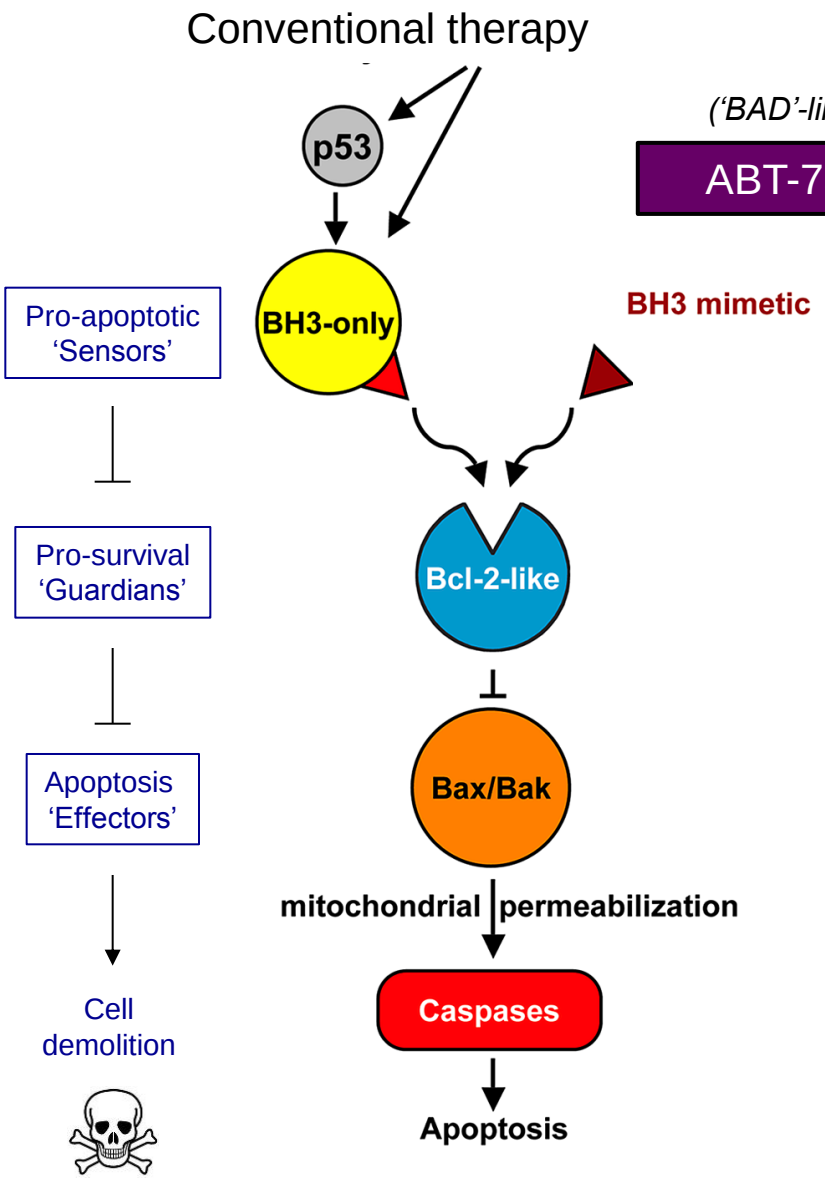
# BCL-2 orchestrates life and death decisions




- BCL-2 is overexpressed in ~75% of breast cancer
- Elevated expression often accompanies chemoresistance

# Targeting BCL-2 in cancer




*('BAD'-like)* ABT-737 *or* *(BCL-2 specific)* ABT-199

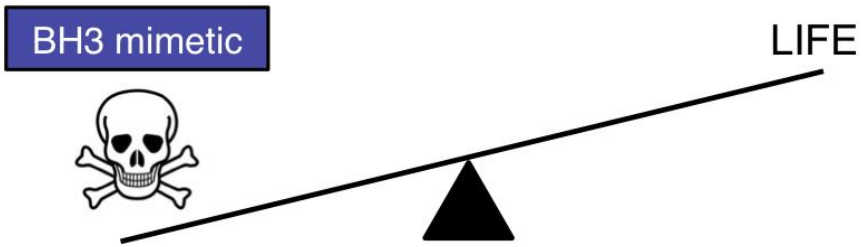
**Potential of BH3 mimetics for cancer therapy:**

Tumour cells resist apoptosis by:

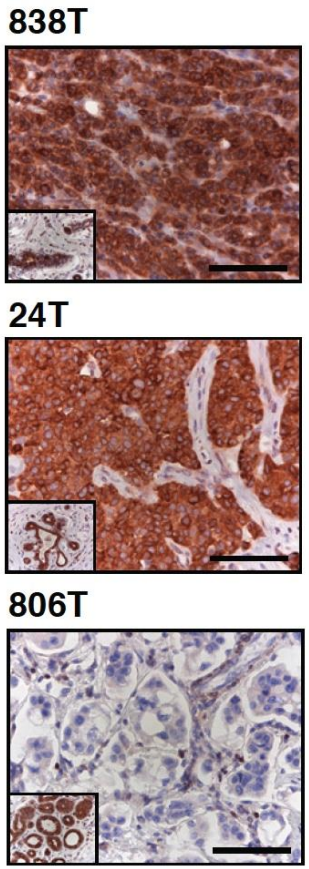
- Over-expression of pro-survival Bcl-2 proteins
- Defective induction of BH3-only proteins, eg p53 mutation

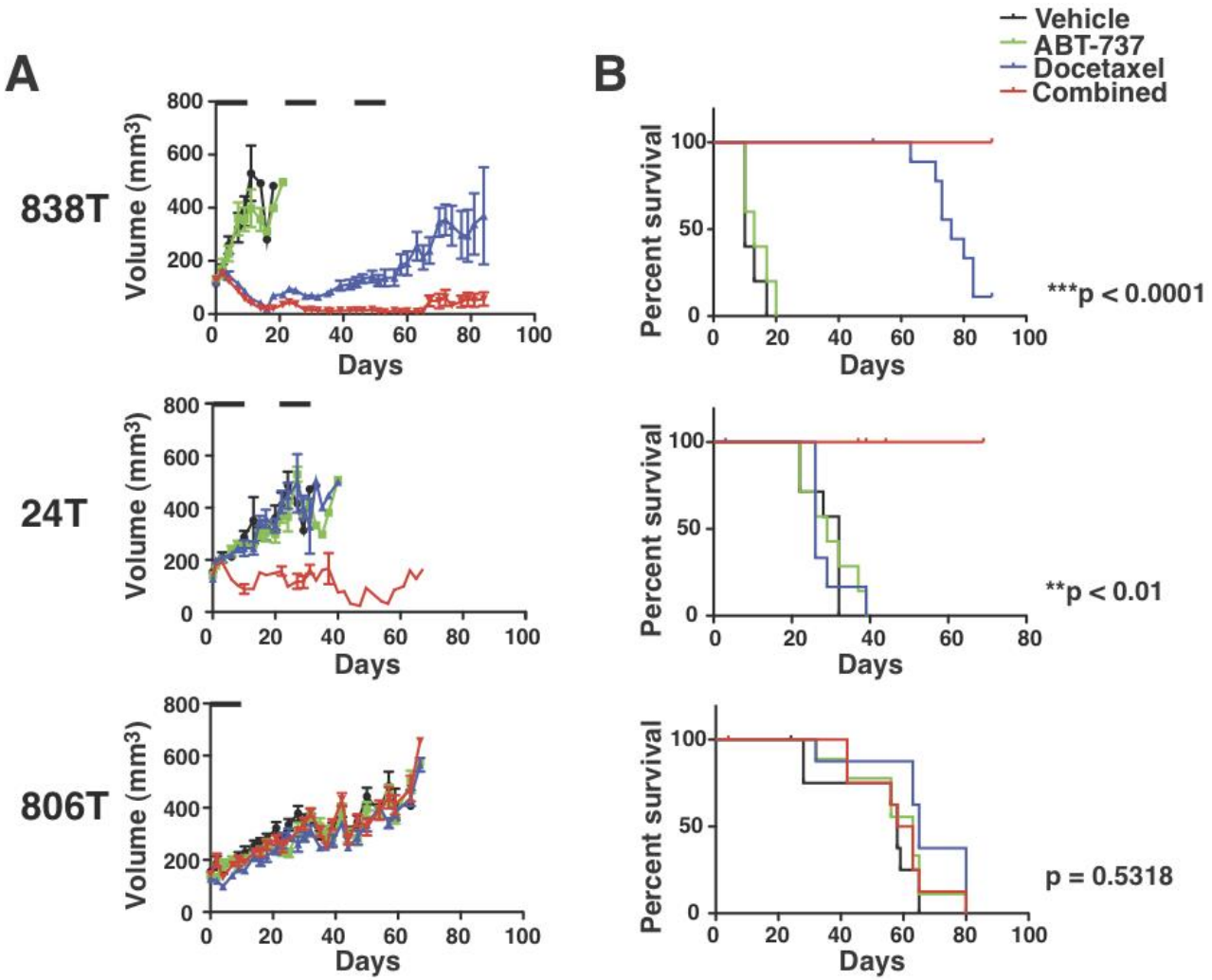
A 'BH3 mimetic' should overwhelm the pro-survival proteins and induce apoptosis

- Acts downstream of p53



# The BH3 mimetic ABT-737 sensitizes TNBC xenografts to docetaxel chemotherapy

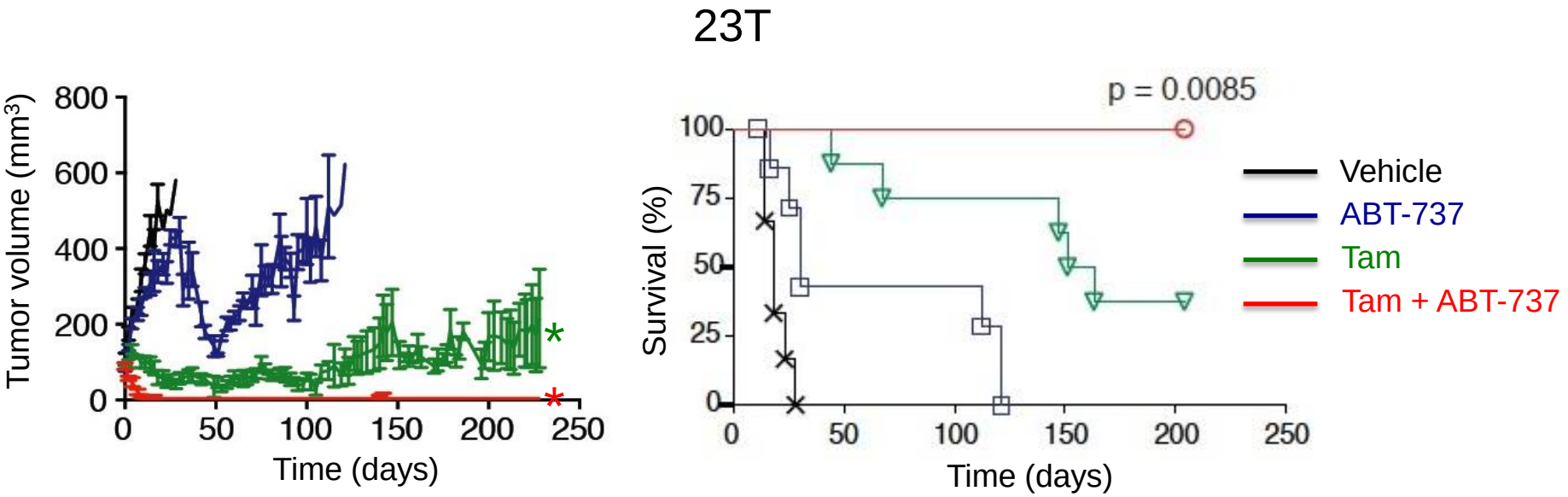


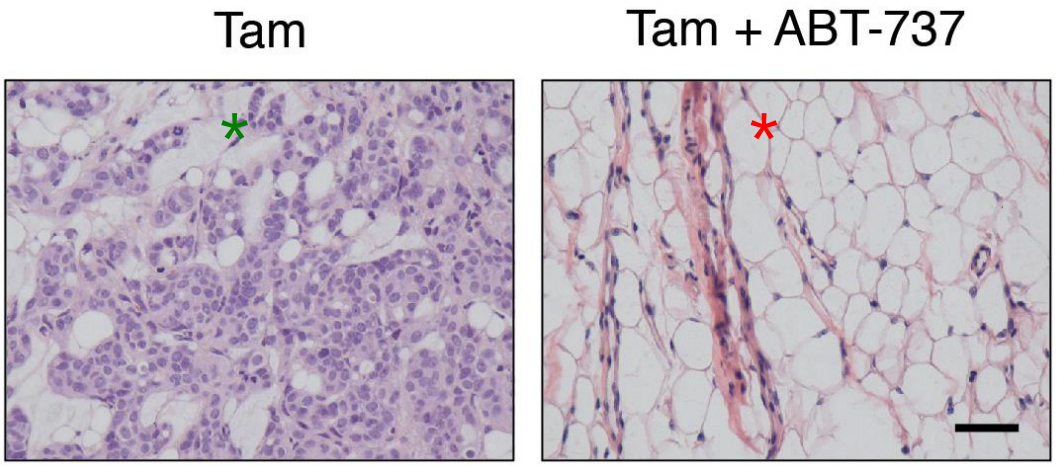




Samantha Oakes, François Vaillant

Oakes et al *PNAS* 2012

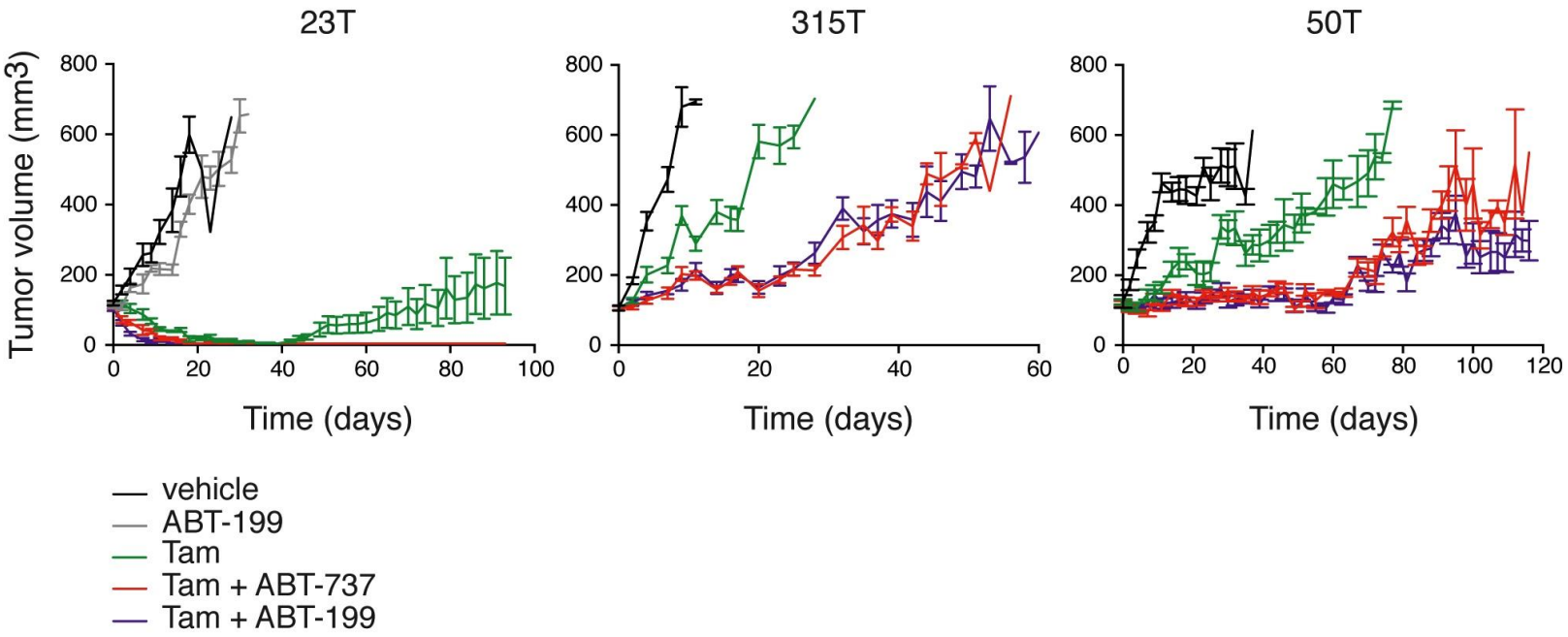
# ABT-737 augments tamoxifen tumour response




*Log-rank (Mantel-Cox) Test*

# The BCL-2 specific inhibitor ABT-199 is also effective in combination with endocrine therapy




*'Proof-of-principle' pre-clinical findings that justify transfer to the clinic?*

Vaillant et al, *Cancer Cell* 2013

# Dual targeting of the BCL-2 and PI3K/AKT/mTOR pro-survival pathways is tolerable and effective

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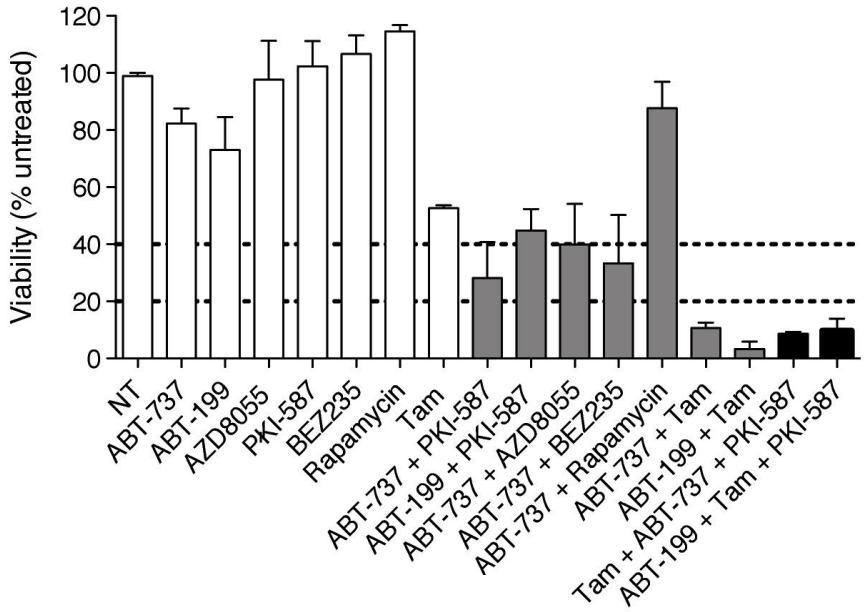
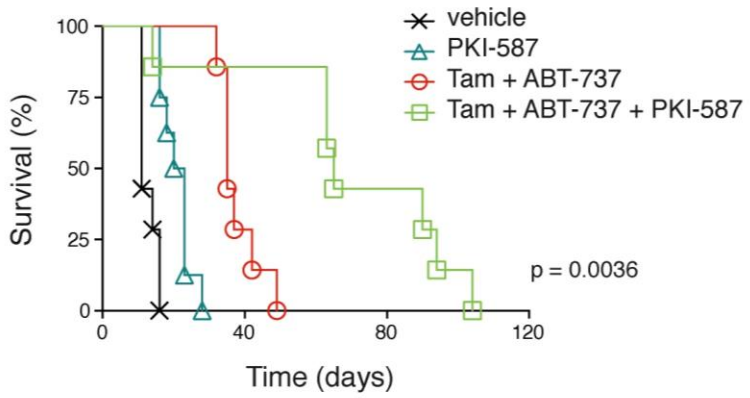
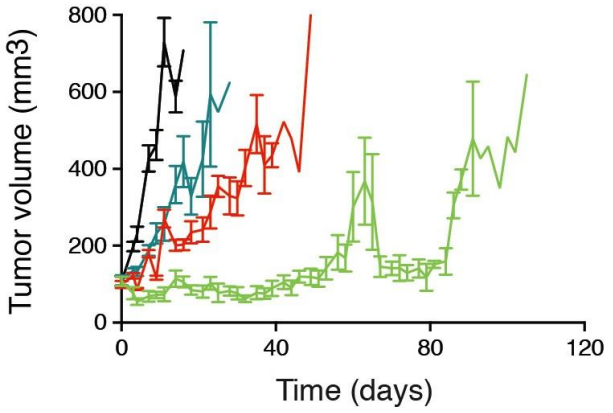
Xenograft

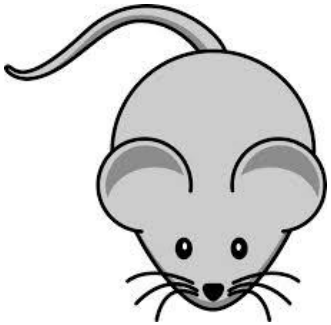



Vaillant et al, *Cancer Cell* 2013

# Xenograft models of solid tumours – future directions



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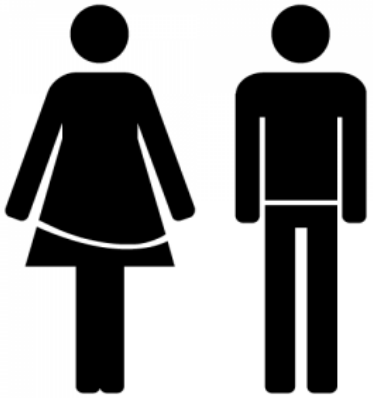

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A powerful new research tool to

- Study tumour behaviour
- Reveal the potential utility of novel therapies
- Evaluate ‘personalised’ therapy based on distinct genomic features of the tumour

## WEHI – BCL

Jane Visvader

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Kelsey Breslin
Bianca Capaldo
Naiyang Fu
Lily Lee
Tamara McLennan
Delphine Merino
Ewa Michalak
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