



Introducing the X-MAN™

Patient-relevant 'mutant and normal' isogenic human cancer cell-lines



Discovery 1 X-MAN™

Single mutated cancer gene panel

NORMAL BREAST EPITHELIUM

Knock-ins and knock-outs:

- B-Raf (knock-in V600E)
- PI3Ka (knock-in H1047R)
- PI3Ka (knock-in E545K)
- EGFR (knock-in del E746-A750)
- K-Ras (knock-in G13D)
- β-Catenin (knock-in T41A)
- p53 (dominant negative knock-out; R273H)

SW48 COLON CANCER

Knock-in and knock-outs:

- B-Raf (knock-in V600E)
- PI3Ka (knock-in E545K)
- K-Ras (knock-in G13D)
- PTEN (knock-out; R130*)
- PI3Ka (knock-in H1047R)
- p53 (dominant negative KO; R273H)

NB: SW-48 parental is WT for the KI-genotypes

HCT116 COLON CANCER*

Knock-in and knock-outs:

- p53 (knock-out)
- PTEN (knock-out)
- BRCA2 (knock-out)
- SMAD4 (knock-out)
- MLH1 (knock-in of wt allele)
- PI3Ka (knock-out H1047R)
- PI3Ka (knock-out E545K in DLD1)
- β-Catenin (knock-out)
- K-RAS (knock-out G13D)
- B-Raf (knock-out V600E)

Discovery 2 X-MAN™

Double mutated cancer gene panel

NORMAL BREAST EPITHELIUM

Double knock-ins:

- EGFR (del E746-A750) & BRAF (V600E)
- K-Ras (G13D) & PI3Ka (H1047R)
- PI3Ka (H1047R) & EGFR (del E746-A750)
- PI3Ka (H1047R) + B-Raf (V600E)
- EGFR (del E746-A750) & KRAS (G13D)

X-MAN™ Researcher

Cancer associated/modifier gene panel

HCT116 COLON CANCER*

Single or double knock-outs:

- 14-3-3 Sigma; 14-3-3 Sigma/p21; ATR (DLD1);
- Bax; Bax/p21; BLM; CDC4 (HCT116 & DLD1);
- CHK2; Dicer (HCT116, DLD & RKO); DNMT1;
- DNMT 1 and 3b; FANCC (RKO); FANCG (RKO);
- HAUSP; MKK4 (panc 04.03); MTAP;
- P16+DNMT1/3b; p21 (HCT116 and DLD-1);
- PPARδ; PUMA; PUMA/p21; Securin;
- SMAC/Diablo; XIAP (HCT116 and DLD-1);
- MEK

*Unless otherwise stated ■ In Development

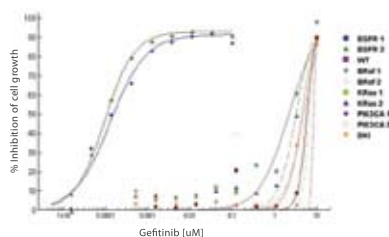
What are X-MAN™ cell-lines?

- ▶ Library of >90 genetically-defined and isogenic human cell-line pairs
- ▶ Genetically identical except knock-in or-out of cancer causing mutation
- ▶ Highly patient-relevant DNA mutations introduced to endogenous genes
- ▶ Definitive tools for studying cancer vs. normal cell biology & drug responses
- ▶ Produced using GENESIS™ - a patented virally-mediated gene engineering technique

Applications in drug discovery

- ▶ Identify & validate patient-relevant targets
- ▶ Identify selective compounds earlier
- ▶ Match drug to responsive patient populations
- ▶ Design shorter, patient-relevant clinical trials
- ▶ Find diagnostic and predictive biomarkers
- ▶ Determine 'on' vs. 'off' target effects

Isogenics in action: Patient-profiling

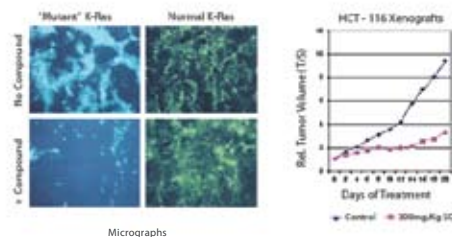


Proof-of-concept showing how Gefitinib (a marketed cancer drug) targets patients carrying specific mutations in the EGFR-receptor. Patient-types were modelled by creating isogenic cell-lines harbouring normal (black); EGFR (green) and various other mutations (other colours). These findings closely match the clinical outcome.

DKI comprises EGFR & secondary mutation known in clinical trials to reverse Gefitinib sensitivity to EGFR.

*Patent pending on patient profiling using in-vitro pharmacays

Isogenics in action: Drug screening



Proof-of-concept: Direct screen for selective drug candidates from library of 30,000 compounds using isogenic cell-lines. Two novel agents identified with selectivity for mutant Ras. One of these compounds was successfully taken into in vivo studies.

See Torrance et al., Nature Biotechnology, 2001.

*Patent pending on isogenic screening applications

Caliper Discovery Alliances & Services

CDAS offers a wide range of products using X-MAN cell-lines

- ▶ Cell-line Licensing: For Evaluation, R&D, Screening, Clinical-Trial Design
- ▶ Custom Engineering: Design Your Own X-MAN Cancer Models
- ▶ Compound Screening & Profiling: Short-cut Activity Screens, Patient Selectivity Profiling
- ▶ Strategic Partnerships: Custom Programs combining CDAS Oncology Service Platforms



CALL CDAS TODAY

Please call Philippe Mourere +44 (0) 7917 620377 or send an e-mail to CDASin vitro@caliperLS.com to discuss your specific research and development needs.



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