Finding Cancer’s Vulnerabilities

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Hereditary diffuse gastric cancer (HDGC)

Family A
HDGC is caused by inherited mutations in the E-cadherin gene (*CDH1*)
>350 families worldwide
HDGC Clinical Management Guidelines

Genetic testing, age >16yrs

CDH1 mutation positive

If unwilling for surgery, preferring to delay, or <20yrs

Surveillance endoscopy

Biopsy +ve

Biopsy -ve

Repeat annually

(Prophylactic) total gastrectomy

Age >20yrs

• Nutritional followup
• LBC screening from 35yrs
• CRC screening in families with history
Family A deaths from stomach cancer

- 1962-1971: 5 deaths
- 1972-1981: 4 deaths
- 1982-1991: 6 deaths
- 1992-2001: 7 deaths
- 2002-present: 1 death
Drug development needs for *CDH1* mutant cancers

- An alternative to total gastrectomy for inherited stomach cancer families
- Treatment for sporadic cancers with *CDH1* mutations
  - 400,000 cases of stomach cancer/yr
  - 150,000 cases of lobular breast cancer/yr
Finding the vulnerabilities

*CDH1* mutations reduce the E-cadherin levels in the cell

What's the target?
Identical human cell lines plus/minus E-cadherin

Control
membrane protein  
E-cadherin

- Genetic screen
  (18,000 genes)

- Known drug screen
  (5,000)

+ Compound screen
  (114,000)
Entinostat (MS275)

Dose dependent effect of MS275 in MCF10A cells

Dose dependent effect of MS275 in MCF10A CDH1-/- cells

E-cadherin +

E-cadherin -

0.3-2.5uM
Novel compounds:

- 114,000 drug-like compounds
- 84 compounds show increased kill on CDH1-/- cells
Loss of E-cadherin creates multiple vulnerabilities that can be exploited with drugs

• Inherited gastric cancer prevention
• Treatment of advanced gastric and lobular breast