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The identification of new drugs for the treatment and prevention of diffuse gastric cancer using high throughput compound screening approach.

Parry Guilford
Centre for Translational Cancer Research
University of Otago
Dunedin, New Zealand

Introduction

HDGC is caused by germline mutation of the E-cadherin gene (*CDH1*). The same gene is mutated in the majority of sporadic (i.e. non familial) diffuse gastric and lobular breast cancers.

The overall logic of this and related projects is that E-cadherin loss will cause vulnerabilities somewhere in the cancer cell which can be exploited with drugs. If we can find those weak points, we have a way of preferentially killing cancer cells that lack E-cadherin (while causing minimal damage to surrounding healthy cells). The overall programme is designed in three waves to ensure our chance of success. The three parts are:

1. Identify existing drugs that are particularly toxic towards *CDH1*-negative cells
2. Identify novel targets (vulnerabilities) in *CDH1*-negative cells, then design drugs that hit those targets.
3. Identify new compounds that preferentially kill *CDH1*-negative cells.

Part 1 is well under way with funding from New Zealand charities and the University of Otago. We have identified 5 classes of drugs that look promising. We are in the middle of validating those drugs with some more in vitro assays. We will then begin investigating clinical trials for both chemoprevention of HDGC and treatment of diffuse gastric and other cancers. The identification of these drugs also gives us proof of principle for our idea, i.e. E-cadherin loss does create exploitable vulnerabilities in the cell.

Part 2 is also progressing well, with major funding (\$NZ910,000) from the New Zealand Health Research Council. We have identified a long-list of around 200 genes/proteins that may be suitable targets for drug development. We'll be validating a few of these over the next year then looking to design drugs against them.

We have received \$20,000 from the DeGregorio Family Foundation to support Part 3. However, the estimated cost of the project is in excess of \$40,000. We are therefore seeking co-funding from NSFC (\$20,000) to enable us to begin this project.

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Research Plan (Part 3)

We propose to screen a library of 110,000 compounds to identify which preferentially kill *CDH1*-negative cells. Top hits will then move into pre-clinical testing (cell lines / mouse models etc.), before clinical trials (although these latter steps will require external funding-perhaps from pharmaceutical companies). The drug screen will be carried out at a specialist lab in Melbourne, Australia: http://www.wehi.edu.au/faculty/advanced_research_technologies/high_throughput_chemical_screening/. The 110,000 compound library they use is carefully selected to avoid compounds that could never be used clinically (some places offer million compound screens but most of the chemicals are junk, i.e. unusable clinically, unstable or not particularly distinct from other compounds in the screen).

How will the drugs help?

We expect the drugs to work on any tumour with a *CDH1* mutation, or low *CDH1* expression or activity. That includes sporadic Diffuse Gastric Cancer (DGC) and Lobular Breast Cancer (LBC), and also many other cancers which tend to lose *CDH1* late in the development. For example, I have a student searching through data on children's cancer to try to find a subgroup that has low *CDH1*. We would then look to applying the drugs we've already found, and anything new we discover in Part 3, to those tumours too.

For Hereditary Diffuse Gastric Cancer (HDGC) the possibilities are two fold – one is to treat all tumours (breast or gastric) and the other is to use it in chemoprevention – that is, to prevent cancer development.