Transforming existing drugs; one more step in the fight against cancer

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Cancer was the most common cause of death for both males and females in New Zealand in 2011, accounting for nearly a third of all deaths.

The most commonly registered cancer was colorectal (3030 registrations), followed by prostate cancer (3023 registrations), together accounting for 28.8% of registrations. Breast cancer and melanoma were the next most commonly registered cancers.
Raloxifene is a Selective Estrogen Receptor Modulator

- Non-steroidal ligand of the estrogen receptor
- Has estrogen-like effects in some tissues (bone)
- Blocks estrogen effects in other tissues (breast, endometrium)
- Evista® (raloxifene HCl 60 mg/day) is approved for the prevention and treatment of osteoporosis
Raloxifene is approved for the prevention and treatment of osteoporosis

- 5.2 fewer fractures per 1000/yr
- 43% decreased risk
Poor bioavailability (~2% due to extensive metabolism by glucuronidation in intestine and liver)

SMA micellar formulation results in:

- High water solubility
- Higher concentration in the plasma by protection from metabolic enzymes
- Enhanced tumor (inflammatory tissues) concentration due to enhanced permeability in these tissues
Enhanced Permeability and Retention Effect in inflammation and cancer

Effect of raloxifene on apoptosis in breast cancer cells in vitro

A

![Graph showing apoptosis in MDA-MB-231 cells](image)

B

![Graph showing apoptosis in MDA-MB-468 cells](image)

SMA-raloxifene reduces tumor spheroid viability

Control  |  Ral 2 µM  |  Ral 5 µM  |  Ral 10 µM  |  Ral 15 µM

SMA      |  SMA-Ral 2 µM  |  SMA-Ral 5 µM  |  SMA-Ral 10 µM  |  SMA-Ral 15 µM

Activity of acid phosphatase, % of control

SMA-Raloxifene enhances intracellular drug accumulation in tumor cells

SMA-raloxifene alters the expression of proteins essential for tumor proliferation and survival

<table>
<thead>
<tr>
<th>Ral (µM)</th>
<th>Ral</th>
<th>SMA-Ral</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
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</tr>
</tbody>
</table>

- VEGFR2
- VEGFR2 Fragments
- EGFR
- Phospho-AKT
- AKT
- Phospho-SRC
- SRC
- Focal Adhesion Kinase
- NFκB
- Cyclin E2
- Cox-2
- β-tubulin

SMA-raloxifene suppresses angiogenesis

Huvec

Control
Ral 5 μM
SMA-Ral 5 μM

Rat aortic ring

Control
Ral 5 μM
SMA-Ral 5 μM
SMA-raloxifene reduces the growth of PC3 xenograft prostate tumours

- Vehicle
- Ral 1 mg/kg
- Ral 5 mg/kg
- SMA-Ral 1 mg/kg

SMA-raloxifene reduces the growth of MDA-MB-231 breast tumours

I.V. injection

Tumour volumes (mm³)

Control
Raloxifene 1mg/kg
SMA-Raloxifene 1mg/kg
SMA-Raloxifene 0.5mg/kg

Time (d)

*p<0.05

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Cannabinoids for management of cancer


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• WIN 55,212-2 is a potent cannabinoid receptor agonist that has been found to be a potent analgesic in neuropathic pain
  - Poorly water soluble
  - Target both CB1 and CB2
  - Side effect;

➢ Psychoactive effects

*[include euphoria, alteration of sensory perception, sensation of relaxation / calmness, loss of sense of time and space, higher perception of colour and sound, and flight of ideas]*
Cytotoxicity of Free and Micellar WIN55-212 on MDA-MB-231 cells

- **free win**
- **micelle win**

Percentage of control vs. concentration (µM)

Cytotoxicity of Free and Micellar WIN55-212 on PC3 cells

Percentage of control vs concentration \( \mu \text{M} \)

- Free win
- Micelle win
Why Oral Chemotherapy

- Non-invasive - reduces patient trauma
- Sustained pharmacokinetic profile
- Economical
- Interest to the pharmaceutical industry

- Most anticancer drugs exhibit poor oral bioavailability
  Paclitaxel on oral administration showed less than 1% bioavailability.
Oral Anticancer Nanomedicine

- Nanocarrier protects the drug from harsh GI environment
- Reduced toxicity
- Can increase oral absorption
- Tumor targeting through EPR effect

To date - No Oral Anticancer Nanomedicine in clinical use.
Tumor accumulation of oral SMA- micelles in tumor tissues

Oral gavage of free Dil

Oral gavage of SMA-Dil

Intravenous SMA-Dil

Haematoxylin staining  SMA-Dil Flourescence

Tumor accumulation of oral SMA-micelles in different tissues

Maximum tolerated dose (MTD) of SMA-PTX micelles following oral administration

<table>
<thead>
<tr>
<th>Single dose MTD</th>
<th>MTD in BALB/c mice</th>
<th>PTX (Ebewe)</th>
<th>SMA-PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy female BALB/c mice n = 6</td>
<td>Single dose</td>
<td>60 mg/kg</td>
<td>120 mg/kg</td>
</tr>
<tr>
<td>Mice survival and variation in body weight</td>
<td>Repeated dose (doses)</td>
<td>30 mg/kg</td>
<td>60 mg/kg</td>
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<tr>
<td>Repeated dose MTD</td>
<td>every alternate days for 8 days</td>
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<tr>
<td>Healthy female BALB/c mice n = 4</td>
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Antitumor efficacy of SMA-PTX following oral administration in orthotopic colon cancer model

![Graph and images showing tumor weight and examples of control and treated samples.](otago.ac.nz/cancer-research)
Safety of SMA-PTX following oral administration in orthotopic colon cancer model
Acknowledgments

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