Cell cycle and cancer II: Therapeutic windows for cancer treatment

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### Cancer as a world wide disease

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Number of new cases diagnosed each year</th>
<th>Number of deaths each year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin cancer</td>
<td>53,600</td>
<td>7,400</td>
</tr>
<tr>
<td>(melanoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>169,400</td>
<td>154,900</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>107,300</td>
<td>48,100</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>41,000</td>
<td>8,500</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>205,000</td>
<td>40,000</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>39,300</td>
<td>6,600</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>23,300</td>
<td>13,900</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>189,000</td>
<td>30,200</td>
</tr>
</tbody>
</table>

Statistics are based on estimates made by the American Cancer Society ([www.cancer.org](http://www.cancer.org)), and refer to the 2002 United States population.

### The 20 most common causes of death from cancer

**UK, 2004**

- Lung
- Colorectal
- Breast
- Prostate
- Oesophagus
- Pancreas
- Stomach
- Bladder
- Ovary
- NHL
- Leukaemia
- Kidney
- Brain + CNS
- Liver
- Multiple myeloma
- Mesothelioma
- Melanoma
- Oral
- Body of uterus
- Cervix
- Other

![Graph showing the 20 most common causes of death from cancer UK, 2004](image)

- **Males**
- **Females**

0 10000 20000 30000 40000

Number of deaths
Some of the actual therapies are very effective in cancer treatment:

Examples: Cisplatin in testicular cancer
Tamoxifen in breast cancer

HOWEVER,

Side effects are still considerable and dramatic, such as gastrointestinal and renal deficiency.

This imposes the need for the design and improvement of new drugs.
Oncogene-addiction

Dependence of some tumors on the continued activity of a specific oncogene, even in the presence of additional tumorigenic lesions.

This dependence on (addiction to) for maintaining the cancer phenotype provides an Achilles heel for tumors that can be exploited in cancer therapy.

Design of new therapies

Table 1: Targeted agents and their current status in clinical testing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Disease</th>
<th>Clinical trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (Gleevec)</td>
<td>ABL</td>
<td>CML</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>KIT</td>
<td>GIST</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>PDGFR</td>
<td>HES</td>
<td>Approved</td>
</tr>
<tr>
<td>Getifarnib (Resviteq)</td>
<td>EGFR</td>
<td>Lung cancer</td>
<td>Approved</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>EGFR</td>
<td>Lung cancer</td>
<td>Approved</td>
</tr>
<tr>
<td>COI-770</td>
<td>mTOR</td>
<td>Various cancers</td>
<td>Phase I, II, III</td>
</tr>
<tr>
<td>RAD001</td>
<td>ATM</td>
<td>Breast cancer</td>
<td>Phase I, II</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>EGFR</td>
<td>Lung cancer</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>FLT3</td>
<td>AML</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>MLN-818</td>
<td></td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>CEP-701</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EAY 45-0006</td>
<td>VEGFR</td>
<td>Kidney cancer</td>
</tr>
<tr>
<td></td>
<td>SU11248</td>
<td>VEGFR</td>
<td>Kidney cancer</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukaemia; HES, hypereosinophilic syndrome; CML, chronic myelogenous leukaemia; GIST, gastrointestinal stromal tumours; RAF, retinoblastoma proto-oncogenes.
Resistance in cancer

- **Turnover rate**: 
  - Proliferating tumor cell
  - Quiescent tumor cell
  - Dying tumor cell

- **Mutation rate**: 
  - Non-mutant tumor cell
  - Mutant tumor cell

- **Effective tumor size**: 
  - Cancer stem cell
  - Committed progenitor cell

- **Mutation fitness**: 
  - Drug-sensitive tumor cell
  - Reduced fitness mutation
  - Equivalent fitness mutation
  - Increased fitness mutation

Probability of resistance:

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**Therapy (DNA damage)**: 
- p16

**myc**: 
- ARF
- bcl2

**Senescence**: 
- p53

**Apoptosis**: 
- p53
P53 as a therapeutical target

Tumor

Mutated p53

Normal p53

Activation

Apoptosis

Tumor irradication

P53 as a therapeutical target

Oncogenic stress

Cell-cycle arrest

Apoptosis

Death receptor

Cyto C release

Mitochondria
Mdm2: master regulator of p53

Small-molecule MDM2 inhibitors
**RITA**

*(Reactivation of p53 and Induction of Tumour cell Apoptosis)*

- small molecule that inhibits the growth of a WT p53 colon carcinoma cell line with minimal effect on a cell line without the WT p53.

- RITA increased p53 in human tumour cell lines that expressed wild-type p53 (colon, osteosarcoma and fibro-sarcoma cells), selectively killing them.
Nutlin-3 shows strong anti-tumor effects, and very few side effects on normal tissues.

Loss-function screenings (using RNAi technique) allowed the identification of genes that made cancer cells more sensitivity to Nutlin-3.

This is another way to gain insights on how to improve drugs.

(Dimova and Dyson, 2005)
The E2F-RB Pathway

Tumor cells differ genetically from normal cells
- Loss of tumor suppressor
- Overexpression of an oncogene

Identify genes which upon KD are specifically lethal for tumor cells

Genotype Specific Lethal Screens

siRNA library

- WT

- Loss of tumor suppressor
- Overexpression of an oncogene

... P53/Pten loss

... E2F1 overexpression

Figure adapted from Kaelin, 2005
Molecular signatures

The resulting molecular signatures allow the patients to be classified into groups with a poor prognosis or a good prognosis, thus facilitating therapeutic decision making.
Breast cancer

Chemotherapy and/or hormonal therapy

reduce the risk of distant metastases by approximately one-third

70-80% of patients would have survived without it

more accurate means of prognostication is needed

improve selection of patients
Comparison of survival analysis carried out using gene expression profiling compared to the St. Gallen criteria:

Development of a panel of gene expression signatures that predict sensitivity to chemotherapeutic drugs.
Identification of the oncogenic pathway by molecular profiling of the tumor

Different cell lines with different oncogenes

It is possible to define signatures of the oncogenic pathway

Integration of chemotherapy response signatures with signatures of the oncogenic pathway deregulation

New therapies that best matches the characteristics of the individual

Examples:

A- Cell lines predicted to be resistant to docetaxel have activated PI3-kinase pathway

Profiling of tumors for these pathway will give information on which cancers docetaxel should be used or not

B- Ovarian cell lines that were predicted to be resistant to topotecan had Src pathway deregulated

High probability of topotecan resistance and sensitivity to SU6656 (a drug that inhibits the Src pathway)
**Connectivity Map**

A tool with the potential to change the speed and efficiency of drug discovery:

- Treatment cells with a collection of small compounds
- Recorded gene alterations caused by each of the compounds
- Stored these patterns in data base
- Use pattern matching method to link compounds of unknown function with compounds with known biological targets and functions

Golub and Armstrong groups, Science 2006
Example 1:

**Problem:**

Resistance to dexamethasone in primary acute lymphoblastic leukemia (ALL)

**Use the Connectivity Map:**

Identification that rapamycin can reverse the resistance pattern

**Solution:**

Dexamethasone in combination with rapamycin could be an effective therapy for childhood ALL

Clinical trials
Connectivity map for elucidating biological functions and target pathways

Create a connectivity map of gene expression by compound and genetic perturbations, and use "signature of interest" to query for perturbations with similar or opposite pattern.