Hallmarks of cancer


Tumor progression

Only certain paths are available to tumors as they acquire hallmarks.
Emerging hallmarks

New hallmarks are being proposed by different researchers.
Therapeutic agents

Different hallmarks are associated with different therapeutic agents.
More therapeutic agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Addiction</th>
<th>Hallmarks</th>
<th>Potential mechanisms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>17AAG (small molecule)</td>
<td>HSP90</td>
<td>NOA</td>
<td></td>
<td>A geldanamycin analog that binds to the ATP-binding pocket of HSP90 and inhibits its catalytic activity</td>
<td>Whitesell and Lindquist, 2005</td>
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<tr>
<td>1MT, MTH-Trp (small molecule)</td>
<td>IDO</td>
<td>NOA</td>
<td></td>
<td>Inhibits tryptophan catabolism in tumor microenvironment to allow T cell proliferation</td>
<td>Muller and Scherle, 2006</td>
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<tr>
<td>5-fluorouracil (small molecule)</td>
<td>DNA</td>
<td>NOA</td>
<td></td>
<td>Inhibits pyrimidine metabolism, incorporation into DNA and RNA causes cell-cycle arrest</td>
<td>Longley et al., 2003</td>
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<tr>
<td>ABT-737, ABT-263 (small molecule)</td>
<td>BCL-XL, BCL-2</td>
<td>OA</td>
<td></td>
<td>Bind to the BH3 pocket of Bcl-XL and inhibit its antiapoptotic function</td>
<td>Stauffer, 2007</td>
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<tr>
<td>Alvocidib, PD 0332991 (small molecule)</td>
<td>CDKs</td>
<td>OA</td>
<td></td>
<td>Inhibit CDKs and induce cell-cycle arrest</td>
<td>Lee and Sicinski, 2006</td>
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<tr>
<td>AP 12009 (antisense oligo)</td>
<td>TGFβ 2</td>
<td>NOA</td>
<td></td>
<td>Inhibits tumor autocrine and paracrine signaling, reverses immune suppression in the tumor microenvironment</td>
<td>Muller and Scherle, 2006</td>
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<tr>
<td>AZD2281, AG014699 (small molecule)</td>
<td>PARP1</td>
<td>NOA</td>
<td></td>
<td>Inhibit base excision repair in homologous recombination repair-deficient cancer cells</td>
<td>Bryant et al., 2005; Farmer et al., 2005</td>
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<tr>
<td>Bevacizumab (antibody)</td>
<td>VEGF</td>
<td>NOA</td>
<td></td>
<td>Inhibits endothelial cell recruitment and tumor vasculature</td>
<td>Folkman, 2007</td>
</tr>
<tr>
<td>BE2335 (small molecule)</td>
<td>PI3K</td>
<td>OA</td>
<td></td>
<td>Causes cell-cycle arrest in tumor cells and inhibits tumor angiogenesis</td>
<td>Maira et al., 2008</td>
</tr>
<tr>
<td>Bortezomib (small molecule)</td>
<td>Proteasome</td>
<td>NOA</td>
<td></td>
<td>Inhibits the catalytic activity of 26S proteasome and induces apoptosis</td>
<td>Roccaro et al., 2006</td>
</tr>
<tr>
<td>Celecoxib (small molecule)</td>
<td>COX2</td>
<td>NOA</td>
<td></td>
<td>Reverses immune suppression in the tumor microenvironment, inhibits tumor autocrine and paracrine signaling</td>
<td>Muller and Scherle, 2006</td>
</tr>
<tr>
<td>Cisplatin and analogs (small molecule)</td>
<td>DNA</td>
<td>NOA</td>
<td></td>
<td>Induces DNA crosslinks</td>
<td>Siddik, 2003</td>
</tr>
<tr>
<td>Erlotinib, Gefitinib (small molecule)</td>
<td>EGFR</td>
<td>OA</td>
<td></td>
<td>Inhibit EGFR tyrosine kinase by competing with ATP binding</td>
<td>Sharma et al., 2007</td>
</tr>
</tbody>
</table>

(the list goes on)

“Hallmark automata”

- With increasing numbers of very specifically targeted therapeutic agents being identified, combining them optimally into cocktails and in temporal succession becomes complex.
- We propose a framework to automatically generate therapeutic regimens.
- Represent progression models as Kripke structure / finite automaton.
- Personalize model to specific cancer type and stage of patient.
- Use model to automatically generate therapeutic regimens:
  - Specify therapeutic objective using
    - Temporal logic
    - Cost function to be minimized
    - Combination of the two
  - Generate supervisory controller to achieve therapeutic objective:
    - Model checking
    - Reachability analysis
    - Cost optimization
E.g., $AG\neg h_2$ will yield controllers that

- give drug a plus drug b at state 0, or
- give drug a at state 0 and drug a plus drug c at state 1,

depending, e.g., on the costs of drug b vs drug c
More complex model

E.g., $AG \neg met$ will yield controllers that

- give Rapamycin, or Avastin and 3BP, if the patient comes at early stage
- give Avastin at stage 3 and 4 and PRIMA-1 at stage 9 and 14 if 3BP has high toxicity
- give 3BP at stage 3 and 4 and PRIMA-1 at stage 7 and 12 if the patient’s genome indicates adverse reaction to Avastin
- give PRIMA-1 if the disease status is advanced but unknown
Ideas / extensions

- (Multi-dimensional) costs for drugs, states, observations (biopsies), (violated) properties
- Timing and probabilities for transitions
- Include edges that can be enabled by drugs
- Include indistinguishabilities between states
- Represent model symbolically
  - $\sim$ symbolic model checking
- Generate model automatically from data (GOALIE)
- ...