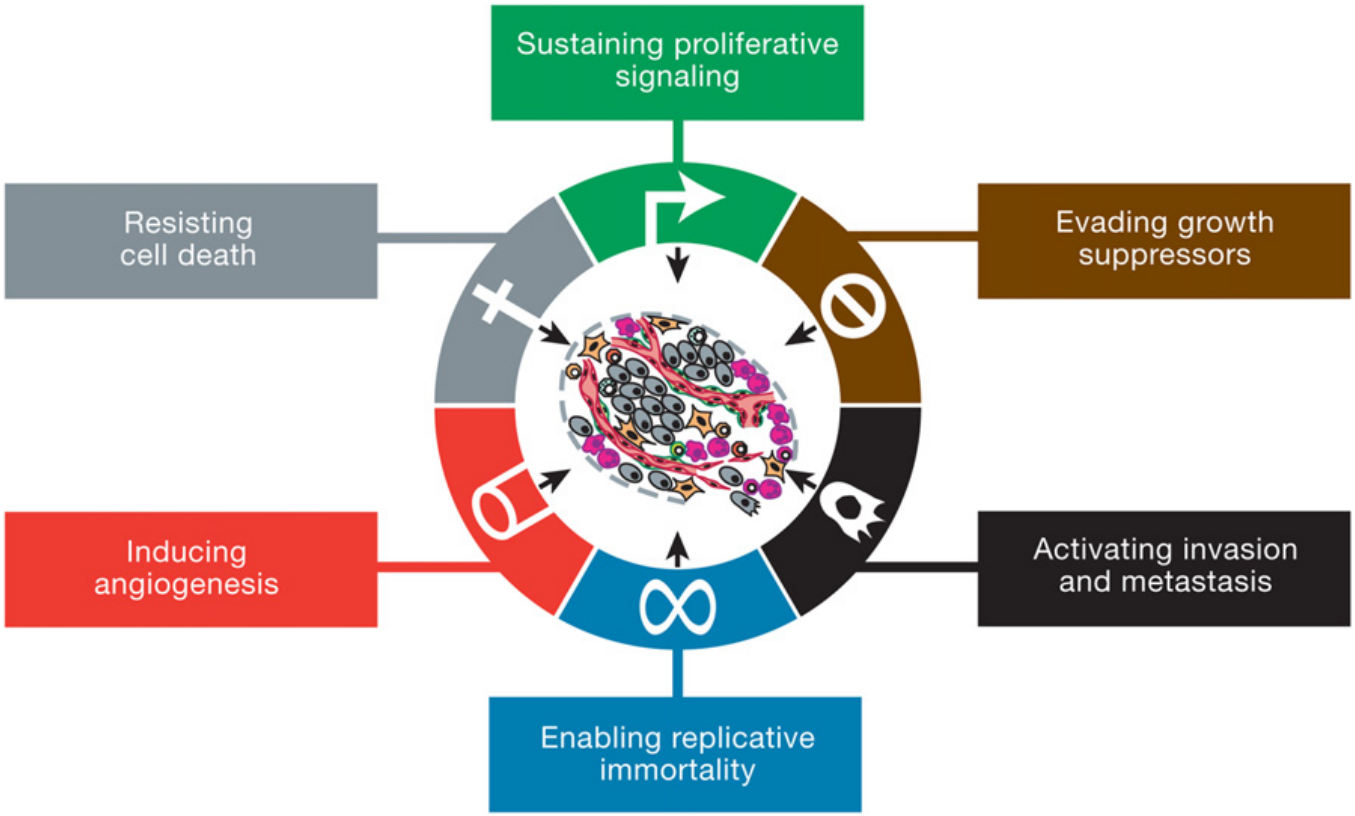
Hallmarks of cancer



D. Hanahan and R. A. Weinberg. *The Hallmarks of Cancer*, Cell, vol. 100, no. 1, pp. 57-70, 2000.

D. Hanahan and R. A. Weinberg. *Hallmarks of Cancer: The Next Generation*, Cell, vol. 144, no. 5, pp. 646-674, 2011.

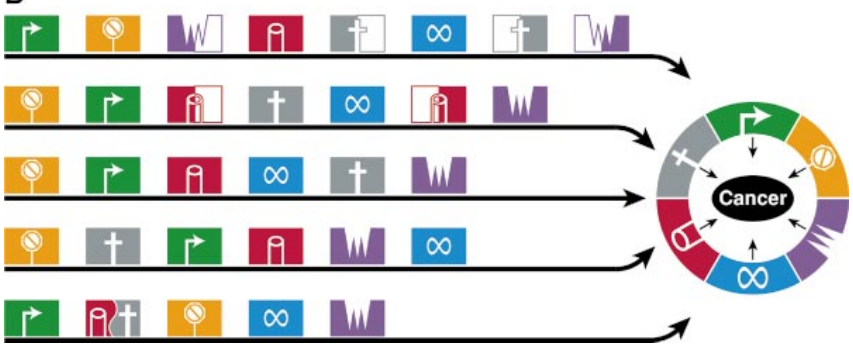
Tumor progression

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

A

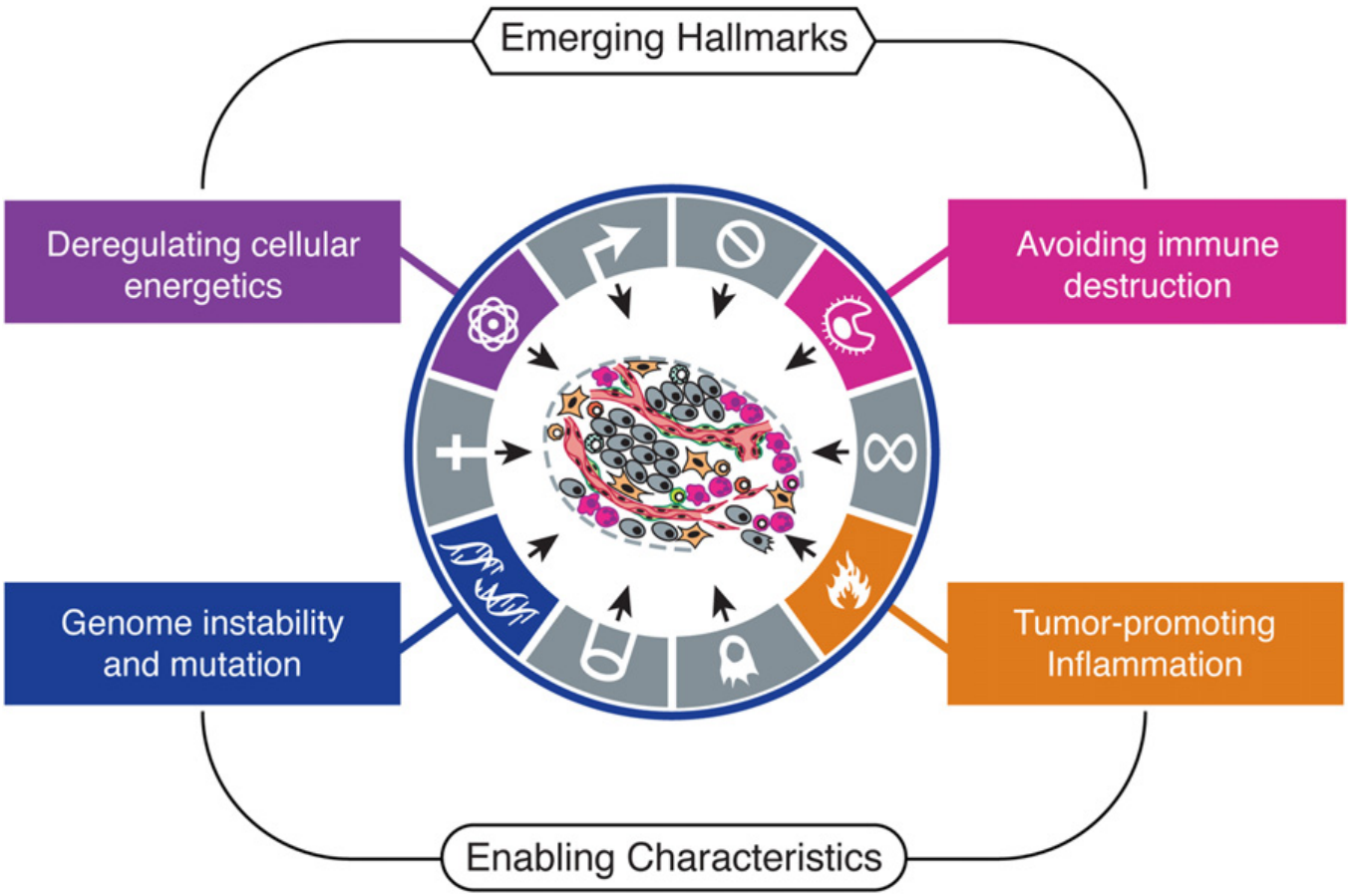
Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin

B



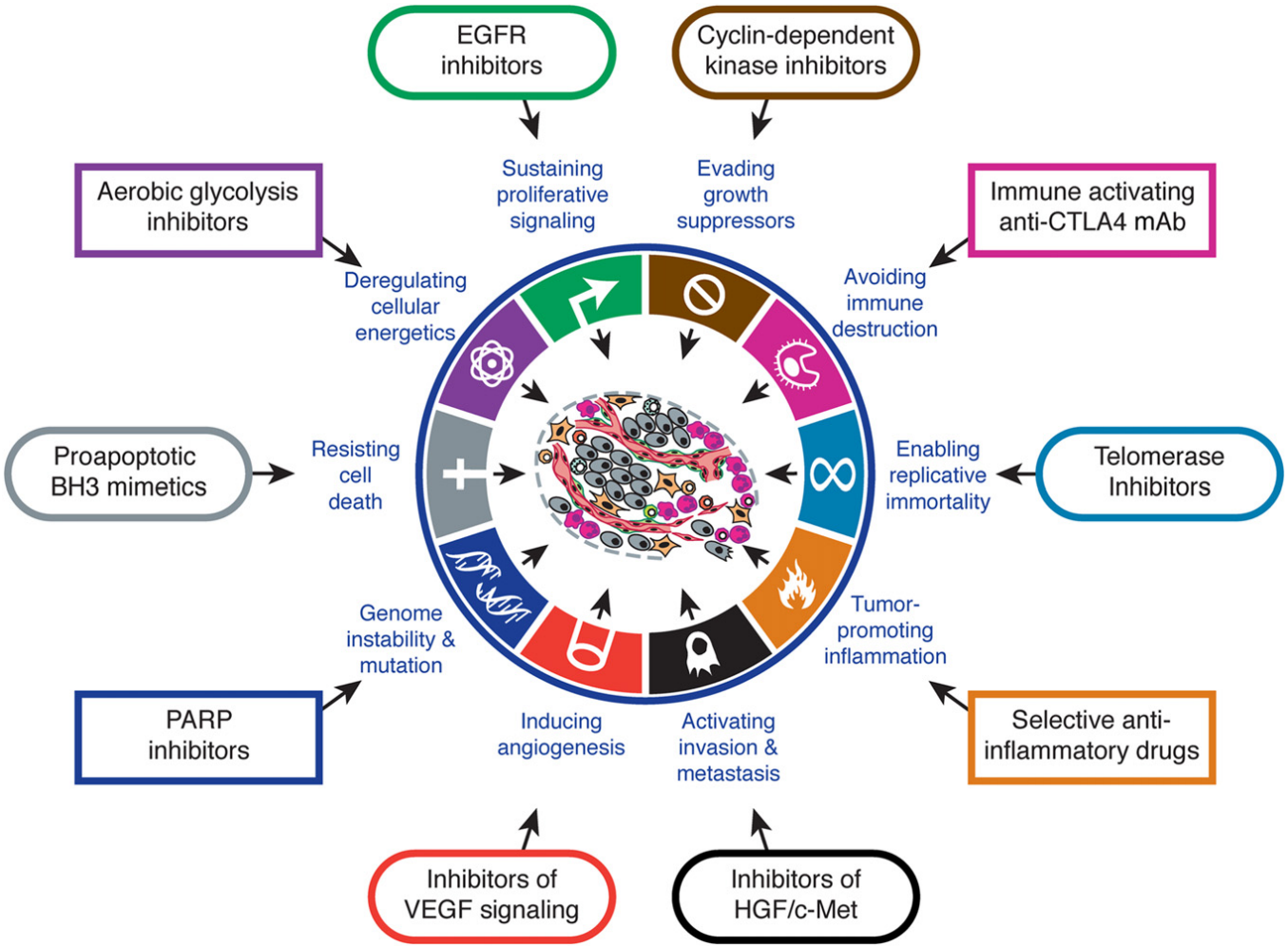
Emerging hallmarks

New hallmarks are being proposed by different researchers.



Therapeutic agents

Different hallmarks are associated with different therapeutic agents.



More therapeutic agents

Agent	Target	Addiction	Hallmarks	Potential mechanisms	References
17AAG (small molecule)	HSP90	NOA		A geldanamycin analog that binds to the ATP-binding pocket of HSP90 and inhibits its catalytic activity	Whitesell and Lindquist, 2005
1MT, MTH-Trp (small molecule)	IDO	NOA		Inhibits tryptophan catabolism in tumor microenvironment to allow T cell proliferation	Muller and Scherle, 2006
5-fluorouracil (small molecule)	DNA	NOA		Inhibits pyrimidine metabolism, incorporation in to DNA and RNA causes cell-cycle arrest	Longley et al., 2003
ABT-737, ABT-263 (small molecule)	BCL-XL, BCL-2	OA		Bind to the BH3 pocket of Bcl-XL and inhibit its antiapoptotic function	Stauffer, 2007
Alvocidib, PD 0332991 (small molecule)	CDKs	OA		Inhibit CDKs and induce cell-cycle arrest	Lee and Sicinski, 2006
AP 12009 (antisense oligo)	TGFβ 2	NOA		Inhibits tumor autocrine and paracrine signaling, reverses immune suppression in the tumor microenvironment	Muller and Scherle, 2006
AZD2281, AG014699 (small molecule)	PARP1	NOA		Inhibit base excision repair in homologous recombination repair-deficient cancer cells	Bryant et al., 2005; Farmer et al., 2005
Bevacizumab (antibody)	VEGF	NOA		Inhibits endothelial cell recruitment and tumor vasculature	Folkman, 2007
BEZ235 (small molecule)	PI3K	OA		Causes cell-cycle arrest in tumor cells and inhibits tumor angiogenesis	Maira et al., 2008
Bortezomib (small molecule)	Proteasome	NOA		Inhibits the catalytic activity of 26S proteasome and induces apoptosis	Roccaro et al., 2006
Celecoxib (small molecule)	COX2	NOA		Reverses immune suppression in the tumor microenvironment, inhibits tumor autocrine and paracrine signaling	Muller and Scherle, 2006
Cisplatin and analogs (small molecule)	DNA	NOA		Induces DNA crosslinks	Siddik, 2003
Erlotinib, Gefitinib (small molecule)	EGFR	OA		Inhibit EGFR tyrosine kinase by competing with ATP binding	Sharma et al., 2007

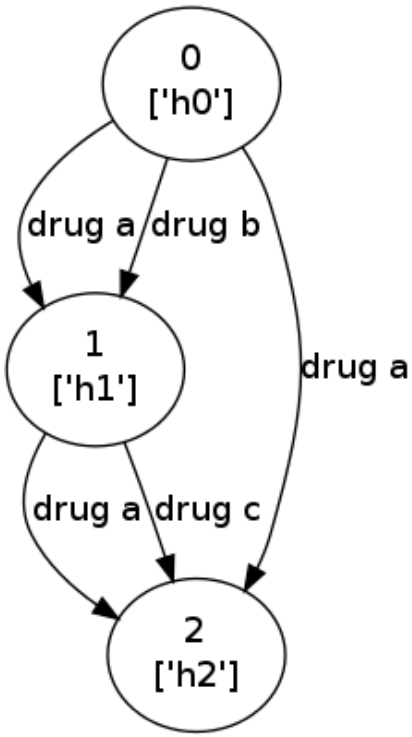
(the list goes on)

J. Luo, N. L. Solimini, and S. J. Elledge. *Principles of Cancer Therapy: Oncogene and Non-oncogene Addiction*, Cell, vol. 136, no. 5, pp. 823-837, Mar. 2009.

"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

Simple example

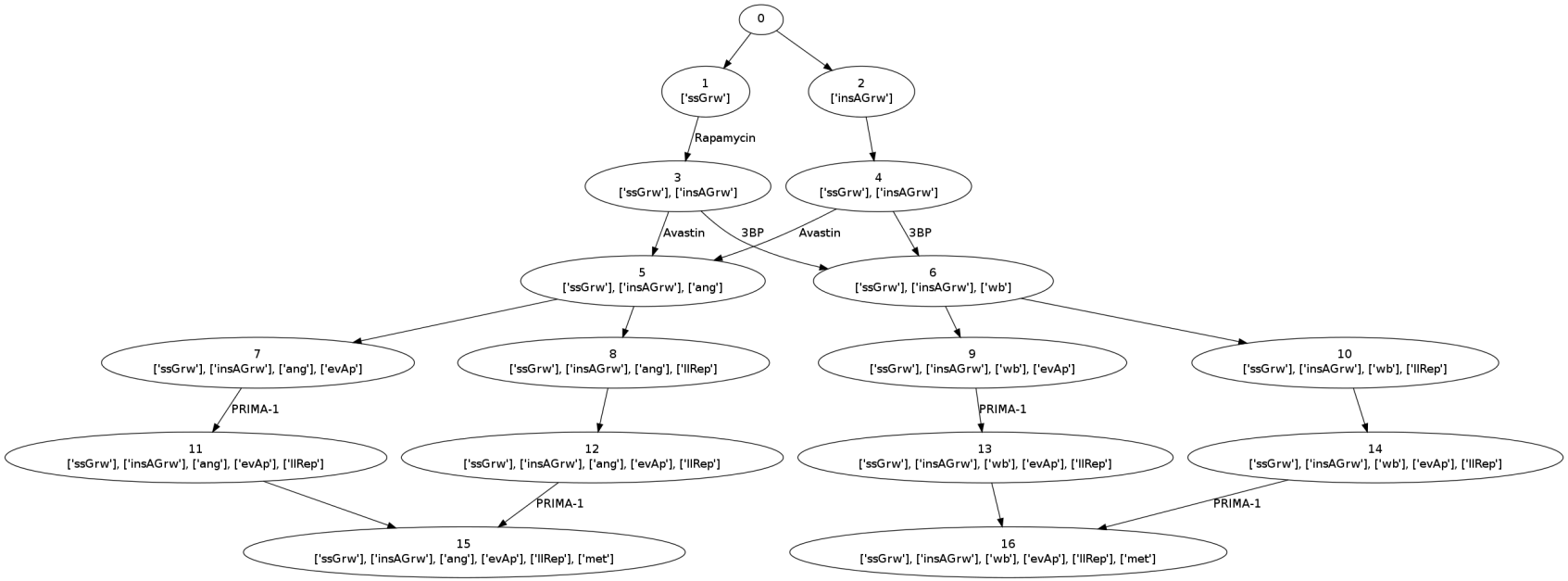


E.g., $AG\neg h2$ will yield controllers that

- 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
  $\rightsquigarrow$ symbolic model checking
- Generate model automatically from data (GOALIE)
- ...