Table 1. Examples of representative cancer biomarkers and their relationship to the hallmark properties of cancer. (Hanahan and Wienberg [Ref. 57]).

Hallmarks of Cancer	Signaling Pathways	Example of Biomarkers	Example of a Major Therapeutic Target
Sustaining proliferative signaling	EGFR/HER IGFR PKC MAPK	Breast cancer: ER PR HER2 p95HER2 IGF-1R/IRS-1 EREG (CRC) IRS1 (BC) IGF2 (CRC) PTEN (BC)	ER HER2
Activating invasion and metastasis	PKC MAPK EGFR/HER IGFR TGF-β	TGFα (CRC) TGFα / Amphiregulin (NSCLC)	EGFR
Evading Growth Suppressors	EGFR/HER MAPK	PTEN (BC)	EGFR
Resisting cell death	IGFR EGFR/HER	IGF2 (CRC) PTEN (BC)	EGFR
Inducing Angiogenesis	VEGF EGFR/HER Ras	VEGF EREG (CRC)	VEGFR
Enabling Replicative Immortality	B-catenin	Telomerase length [14]	

BC: Breast Cancer, CRC Colorectal Carcinoma, NSCLC: Non-Small Cell Lung Carcinoma

Table 2. List of Protein Kinase Inhibitors approved by FDA.
(NRY,nonreceptorprotein-tyrosinekinase;RTK,receptorprotein-tyrosinekinase;S/T,protein-serine/threoninekinase;T/Y, dual-specificityproteinkinase)

Proteinkinaseinhibitor	Approvalyear	Primary targets	Target kinasefamily	Indications
Abemaciclib	2017	CDK4/6	S/T	Breastcancer
Acalabrutinib	2017	BTK	NRY	Lymphoma
Afatinib	2013	ErbB1/2/4	RTK	Lungcancer
Alectinib	2015	ALK,RET	RTK	Lungcancer
Avapritinib	2020	PDGFR	RTK	GastrointestinalCancer
Axitinib	2012	VEGFR1/2/3	RTK	Kidneycancer
Binimetinib	2018	MEK1/2	T/Y	Melanoma
Bosutinib	2012	BCR-Abl	NRY	Leukemia
Brigatinib	2017	ALK	RTK	Lungcancer
Cabozantinib	2012	RET,VEGFR2	RTK	Thyroid.kidney, hepatocellularcancer
Capmatinib hydrochloride	2020	c-MET	RTK	Lungcancer
Ceritinib	2014	ALK	RTK	Lungcancer
Cobimetinib	2015	MEK1/2	T/Y	Melanoma
Crizotinib	2011	ALK,ROS1	RTK	Lungcancer
Dabrafenib	2013	B-Raf	S/T	Melanoma;lung,thyroid Cancer
Dacomitinib	2018	EGFR	RTK	Lungcancer
Dasatinib	2006	BCR-Abl	NRY	Leukemia
Encorafenib	2018	B-Raf	S/T	Melanoma,colorectalcancer
Entrectinib	2019	TRKA/B/C,ROS1	RTK	Lungcancer; solidTumors
Erdafitinib	2019	FGFR1/2/3/4	RTK	Urothelialcarcinoma

Erlotinib hydrochloride	2004	EGFR	RTK	Lung,Pancreaticcancer
Everolimus	2009	FKBP12/mTOR	S/T	Breast,kidneycancer, Neuroendocrinetumors
Fedratinib	2019	JAK2	NRY	Myelofibrosis
Futibatinib	2022	FGFR2	RTK	Cholangiocarcinomas
Gefitinib	2003	EGFR	RTK	Lungcancer
Gilteritinib	2018	Flt3	RTK	Leukemia
Ibrutinib	2013	BTK	NRY	Lymphoma
Imatinib mesylate	2001	BCR-Abl	NRY	Leukemia; Gastrointestinal
Infigratinib	2021	FGFRs	RTK	Cholangiocarcinoma
Lapatinib ditosylate	2007	ErbB1/2/HER2	RTK	Breastcancer
Larotrectinib	2018	TRKA/B/C	RTK	Solidtumors
Lenvatinib	2015	VEGFR,RET	RTK	Hepatocellular,endometrial, Thyroid,Kidneycancer
Lorlatinib	2018	ALK	RTK	Lungcancer
Midostaurin	2017	Flt3	RTK	Leukemia
Mobocertinib	2021	EGFRwith exon 20insertions	RTK	Lungcancer
Neratinib	2017	ErbB2/HER2	RTK	Breastcancer
Nilotinib	2007	BCR-Abl	NRY	Leukemia
Osimertinib	2015	EGFRT790M	RTK	Lungcancer
Pacritinib	2022	JAK2	RTK	Myelofibrosis
Palbociclib	2015	CDK4/6	S/T	Breastcancer
Pazopanib hydrochloride	2009	VEGFR1/2/3	RTK	Kidneycancer;soft tissuesarcoma
Pemigatinib	2020	FGFR2	RTK	Cholangiocarcinoma

Pexidartinib	2019	CSF1R	RTK	Tenosynovialgiantcelltumor
Pirtobrutinib	2023	BTK	NRY	Lymphoma
Ponatinib hydrochloride	2012	BCR-Abl	NRY	Leukemia
Pralsetinib	2020	RET	RTK	Lungcancer
Quizartinib	2023	FLT3/STK1	RTK	Leukemia
Regorafenib	2012	VEGFR1/2/3	RTK	Gastrointestinal,Colorectal, Hepatocellularcancer
Ribociclib	2017	CDK4/6	S/T	Breastcancer
Ripretinib	2020	KIT/PDGFR	RTK	Gastrointestinal cancer
Ruxolitinib phosphate	2011	JAK1/2/3,Tyk	NRY	Myelofibrosis
Selpercatinib	2020	RET	RTK	Lung,thyroid cancer
Selumetinib	2020	MEK1/2	T/Y	Neurofibroma
Sorafenib tosylate	2005	VEGFR1/2/3	RTK	Thyroid,Kidney, Hepatocellularcancer
Sunitinib malate	2006	VEGFR2	RTK	Gastrointestinal,kidney, pancreaticcancer
Temsirolimus	2007	FKBP12/mTOR	S/T	kidneycancer
Tepotinib	2021	Met	RTK	Lungcancer
Tivozanib	2021	VEGFR2	RTK	kidneycancer
Trametinib	2013	MEK1/2	T/Y	Melanoma
Trilaciclib	2021	CDK4/6	S/T	Lungcancer
Tucatinib	2020	ErbB2/HER2	RTK	Breastcancer
Vandetanib	2011	VEGFR2	RTK	Thyroidcancer
Vemurafenib	2011	B-Raf	S/T	Melanoma;histiocyticsarcoma
Zanubrutinib	2019	BTK	NRY	Lymphoma

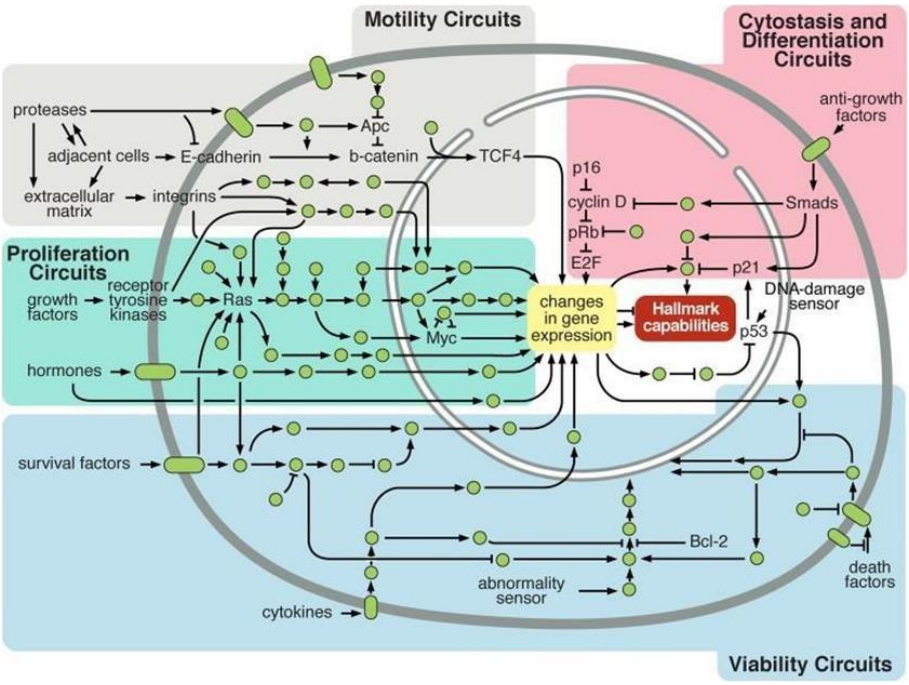

Figure 1. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell.
An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate subcircuits, depicted here in differently colored fields, are specialized to orchestrate various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such subcircuits. In addition, because each cancer cell is exposed to a complex mixture of signals from its microenvironment, each of these subcircuits is connected with signals originating from other cells in the tumor microenvironment. (Hanahan and Wienberg [57]. With permission from Elsevier)

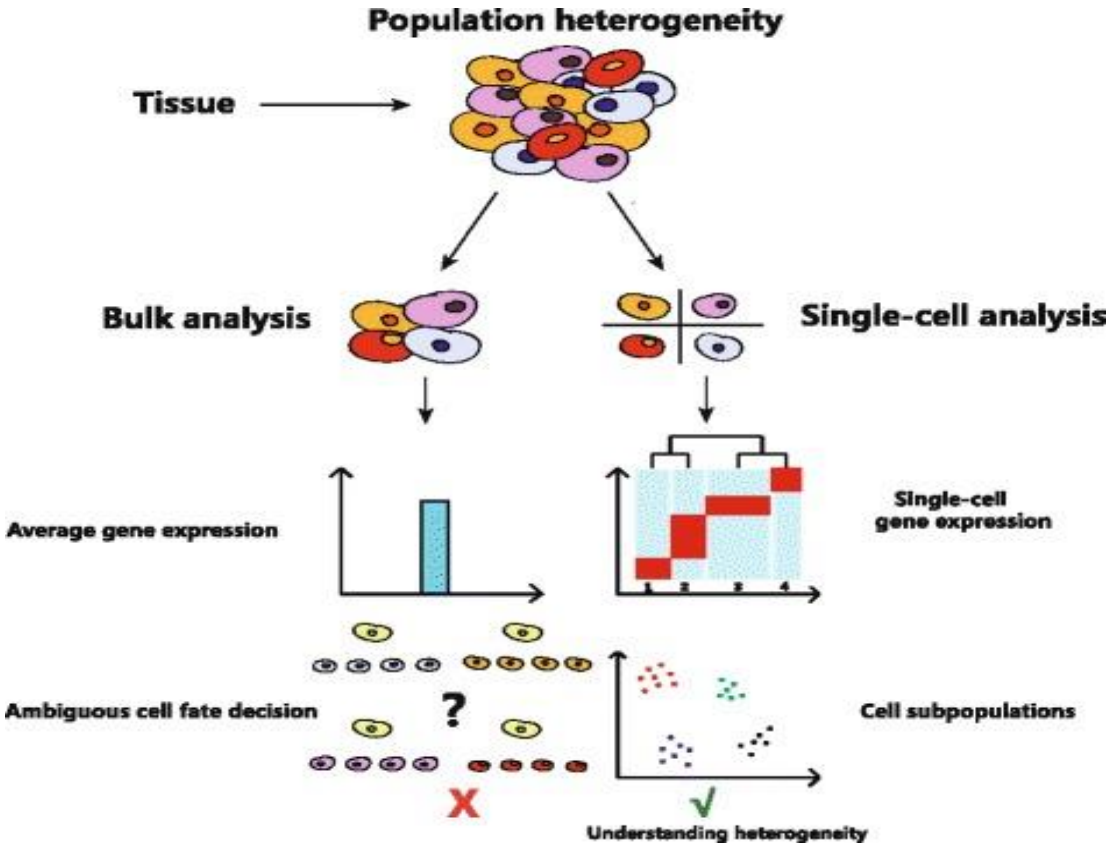

Figure. 2. Single Cell analysis reveals tissue heterogeneity.
Traditional studies on tissue samples mask heterogeneity between individual cells. To understand the heterogeneity of complex tissues, analysis performed on single-cell resolution could be used to unveil cell subpopulations and their gene expression patterns.

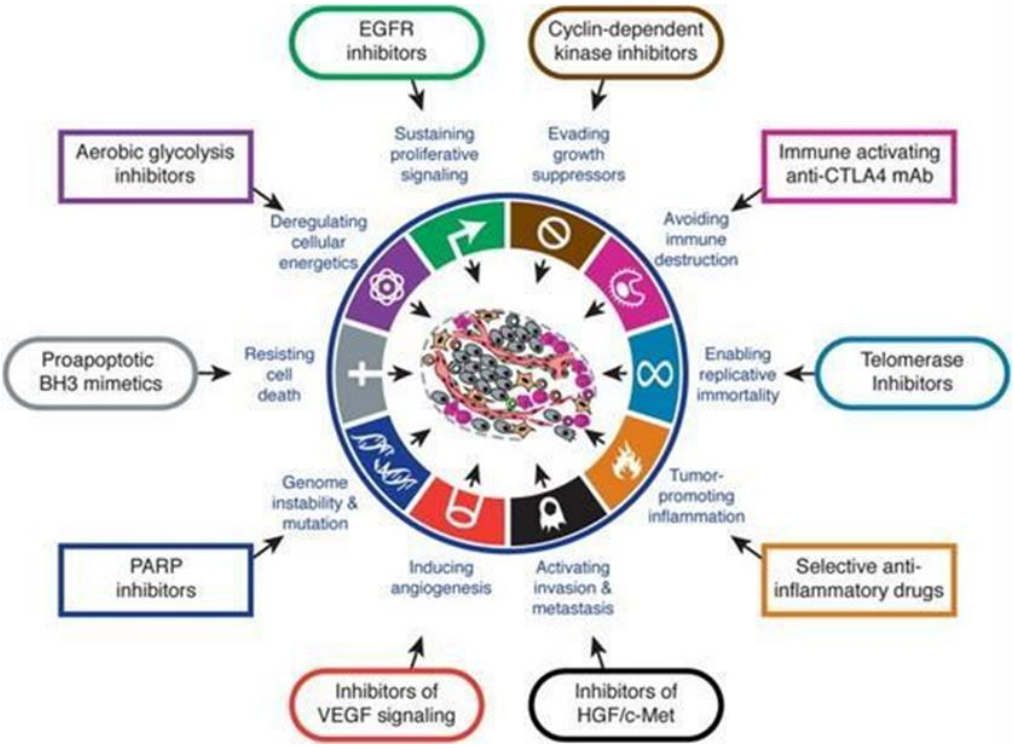

Figure 3. Therapeutic Targeting of the Hallmarks of Cancer

Therapeutic agents that can mitigate the acquired capabilities necessary for tumor growth and cancer progression are being developed for clinical use in treating different cancer types. These drugs are being developed in clinical trials to target each of the emerging neoplastic characteristics and the enabling hallmark capabilities for effective cancer therapy. The listed drugs are illustrative examples; there is a deep pipeline of investigational drugs in development to target different signaling molecules that lead to hallmark capabilities. (Hanahan and Wienberg [57]. With permission from Elsevier)

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