Supplementary Material

The Challenges of Modeling Drug Resistance to Antiangiogenic Therapy

Michalis Mastri[1], Spencer Rosario[2], Amanda Tracz[1], Robin E. Frink[4], Rolf A. Brekken[4] and John M. L. Ebos[1,3,*]

[1]*Department of Cancer Genetics, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY, 142631, USA;* [2]*Department of Pharmacology and Therapeutics, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY, 142631, USA;* [3]*Department of Medicine, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY, 142631, USA;* [4]*Departments of Surgery and Pharmacology, Hamon Center for Therapeutic Oncology Research and University of Texas Southwestern Medical Center, Dallas, Texas, USA*

SUPPLEMENTAL BOX 1: CRITICAL CONSIDERATIONS FOR THIS LITERATURE SEARCH

Several papers required additional considerations/criteria for characterization and grouping for literature analysis. These include:

1) Distinguishing Between Resistance that was 'Derived' *vs.* 'Studied'

Of the 109 papers analyzed, we found that how resistance was *derived* was not always similar to how resistance was *studied*. For instance, some papers described resistant cells that were *derived in vitro* but then later used to *study* resistance mechanisms *in vivo*, or *vice versa*. For example, Zhai *et al.* treated hepatocellular carcinoma cells with increasing concentrations of sorafenib *in vitro* to derive cells, but then implanted these cells ectopically in mice to study the effects of Akt inhibition on resistance [88]. Conversely, Baker *et al.* derived sorafenib resistant cells from acute myeloid leukemia patients but then studied whether sorafenib-resistant FLT3 mutated cells were sensitive to sunitinib *in vitro* [37]. In such instances, we used such designations to separate studies as described in Fig. (**3**) and as outlined in Supplemental Table **1**.

2) Distinguishing Between Acquired or Intrinsic Resistance

Out of the 109 papers, we identified 62 papers that derived resistance by treating cells *in vitro* or *in vivo* until they became non-responsive to treatment over time. These were designated as *acquired* resistance studies. In contrast, we found 50 papers that identified intrinsically resistant cells and used them for study. These included either an initial (failed) treatment effect or a phenotype induced by genetic modification that generated non-responsiveness to therapy. For example, Shojaei *et al.* identified cells with intrinsic sunitinib resistance in implanted tumors *in vivo* [10], whereas Liu *et al.* induced sorafenib resistance in hepatocellular carcinoma cells by overexpressing PROX1 [99]. For this reason, we grouped papers accordingly in our analysis (see Supplemental Table **1** for details).

3) Some Studies Fit into Multiple Categories

Of 109 papers identified in our literature search, we found several studies which could not be sub-grouped easily as they contained multiple classifications or categories (see Fig. **3**; gray areas). For example, Bender *et al.* used sunitinib and sorafenib for their studies [24], Lo *et al.* derived resistance *in vitro* and *in vivo* [100], and Harada *et al.* studied resistance *in vivo* and *in vitro* [74]. Groupings for each study in our analysis are explained in Supplemental Table **1**.

4) Search Criteria did not Identify all Papers

As mentioned in the manuscript, our search results identified 381 publications related to antiangiogenic drug resistance, which was reduced to include only those that met our criteria (detailed in Fig. **1**). In instances where PubMed did not identify all key words, additional papers were added to the final list (total 30). While the final 109 papers identified may not represent a complete list, we feel excluded papers likely do not represent sufficient quantities to alter the general disparities noted in Figs. (**2-4**).

Table S1. Summary of preclinical studies used in analysis.

		Breakdown of drugs used										Breakdown of Models Used to *Derive* Resistance										Breakdown of Models Used to *Study* Resistance									
												Tumor								Non-Tumor			All models						Implantation only			Metastatic only		
												Intrinsic					Acquired			Intrinsic	Acquired												
												in vitro			*in vivo*		*in vitro*	*in vivo*		*in vivo*	*in*	*in vivo*	*in vitro*	*in vivo*						*in vivo*		*in vivo*		
Ref	PMID	Sunitinib (37)	Bevacizumab (18)	Sorafenib (50)	Pazopanib (4)	Axitinib (0)	Cabozantinib (1)	Regorafenib (0)	DC101 (7)	Ziv-Aflibercept (1)	B20/G6-31 (3)	Maniputlated genetically (17)	Known (5)	Discovered (16)	Known (6)	Discovered (11)	Generated (29)	Primary tumor (34)	Metastatic lesions (2)	Discovered (1)	Generated (2)	Primary site (1)	In vitro (78)	Implanted Xenograft (56)	Implanted Syngeneic (11)	GEMM (6)	IV (2)	Other (1)	Orthotopic implantation (14)	Ectopic implantation (59)	PDX (8)	Experimental (2)	Spontaneous-primary removed	Spontaneous-primary intact (16)
1	11859195								x			x												x						x				
2	16226705								x									x								x								
3	17981115								x							x									x					x				
4	19861442	x																x					x											
5	19249680								x									x								x								
6	19318574			x													x						x											
7	20699227	x		x														x						x						x				
8	20501804	x																	x					x						x	x			
9	20406969	x														x									x					x				
10	20952508	x														x							x	x						x				
11	21076618			x														x						x						x				
12	21622725			x					x									x								x								x
13	21737511		x															x					x	x					x					x
14	21436589		x												x			x				x		x					x	x				
15	21407219		x														x						x				x					x			
16	21315783	x													x								x		x					x				
17	21980135	x															x						x											
18	21167632	x																x						x					x	x	x			
19	21982018	x			x									x									x	x						x				
20	21803743		x									x												x							x				x
21	21750552			x													x						x	x						x				
22	21364009		x	x										x									x											
23	21559452			x														x						x						x				
24	22020623	x		x													x						x											
25	22414764			x													x						x											
26	22696593			x										x									x											
27	22447568		x															x					x	x					x	x				x
28	22278289			x										x									x											
29	22484816	x							x									x								x								x
30	22532600	x												x									x	x						x				
31	22783417	x		x										x									x	x						x				
32	22354205			x								x											x											
33	22473773			x										x									x											
34	22269210	x														x								x	x				x	x			x	
35	22180308			x													x						x											
36	22869928	x																x						x						x				
37	23969938	x		x														x					x											
38	23804704		x															x						x						x				
39	23644530		x															x					x	x					x	x				
40	24244338			x													x						x		x				x					x
41	23913124										x		x										x		x					x				
42	23630186	x		x	x									x									x											
43	24113128			x								x		x		x							x	x						x				
44	23623402		x													x							x	x						x				
45	23790465			x										x									x	x						x				x
46	23781255	x		x													x						x											
47	23840364	x																	x				x								x			
48	23316005			x								x											x											
49	23307858		x													x		x						x					x	x	x			x
50	23379954			x										x									x											
51	23361368		x															x						x						x				
52	23299930			x														x					x											
53	23818948	x		x								x											x	x						x				
54	23497256	x																x						x						x				
55	23530240										x				x											x								
56	23804423		x															x					x	x					x					x
57	23839492	x															x	x					x	x						x				x
58	23305097	x															x						x	x						x				
59	23257894			x													x						x											
60	24122794	x																x						x						x				
61	23111106			x													x						x											
62	22983756			x									x										x	x						x				
63	22858906	x		x								x													x					x				
64	23471579			x								x											x		x				x					x
65	23411027			x										x									x											
66	23427299		x															x					x	x						x				x
67	24173109			x								x											x											
68	24529377										x					x							x		x					x				
69	25093491	x																x					x	x			x			x		x		x
70	24723451	x											x										x											
71	23975598	x															x						x											
72	25621299	x															x						x	x						x				

(Table S1) contd….

		Breakdown of drugs used										Breakdown of Models Used to *Derive* Resistance										Breakdown of Models Used to *Study* Resistance										
												Tumor							Non-Tumor			All models						Implantation only			Metastatic only		
												Intrinsic					Acquired		Intrinsic	Acquired		*in vitro*	*in vivo*					*in vivo*			*in vivo*		
												in vitro			*in vivo*		*in vitro*	*in vivo*	*in vivo*	*in*	*in vivo*											
Ref	PMID	Sunitinib (37)	Bevacizumab (18)	Sorafenib (50)	Pazopanib (4)	Axitinib (0)	Cabozantinib (1)	Regorafenib (0)	DC101 (7)	Ziv-Aflibercept (1)	B20/G6-31 (3)	Maniputated genetically (17)	Known (5)	Discovered (16)	Known (6)	Discovered (11)	Generated (29)	Primary tumor (34)	Metastatic lesions (2)	Discovered (1)	Generated (2)	Primary site (1)	In vitro (78)	Implanted Xenograft (56)	Implanted Syngeneic (11)	GEMM (6)	IV (2)	Other (1)	Orthotopic implantation (14)	Ectopic implantation (59)	PDX (8)	Experimental (2)	Spontaneous-primary removed	Spontaneous-primary intact (16)
73	25319392		x														x				x		x										
74	24356934			x													x						x		x					x			
75	25587220	x															x				x		x										
76	24628546				x												x						x	x						x			
77	24333721									x								x							x					x			
78	24240114		x												x								x	x					x				x
79	25015210		x													x							x	x						x			
80	25017961			x								x											x										
81	24716227			x								x											x										
82	24726537			x										x									x										
83	24475095	x										x					x						x										
84	25088418								x									x								x							
85	25216638			x								x															x							
86	25047655			x													x						x	x						x			
87	25531114			x								x											x	x						x			
88	24705351			x													x						x	x						x			
89	24619500			x													x						x										
90	24486412			x										x									x	x						x			
91	25519701	x															x	x					x	x						x			
92	25381264	x																x						x						x	x			
93	25381153		x															x						x					x	x	x			
94	25053293			x										x	x								x	x						x				
95	25663899	x											x							x			x											
96	25855496				x								x		x								x	x					x				x	
97	25908587			x														x						x					x					x
98	26219898						x										x						x											
99	25684142			x								x											x	x						x				
100	25902734			x													x	x					x	x						x	x			
101	25976987			x													x						x											
102	26172295			x								x					x						x	x						x				
103	25519148		x															x						x						x				
104	25769726															x							x	x						x				
105	26114873	x																x						x						x	x			
106	25501128	x														x							x	x						x				
107	25885470			x										x									x											
108	25850433			x													x						x	x						x				
109	25675297	x										x											x	x						x				x

Classification of 109 papers used for analysis based antiangiogenic drugs used and methods used to derive and study resistance. Notes: Studies involving intrinsic resistance were sub-divided into those generated by genetic modification or those found non-responsive to treatment in previous ('known') or current ('discovered') studies. Studies involving acquired resistance included those derived *in vitro* or *in vivo* following chronic or escalating drug doses ('generated'). See Fig. (**1**) for complete list of drugs and drug names used in search. GEMM, Genetically Engineered Mouse Model; PDX, patient-derived xenograft; IV, intravenous.

REFERENCES

[1] Yu JL, Rak JW, Coomber BL, Hicklin DJ, Kerbel RS. Effect of p53 status on tumor response to antiangiogenic therapy. Science. 2002; 295(5559):1526-8.

[2] Casanovas O, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. Cancer cell. 2005; 8(4):299-309.

[3] Fischer C, Jonckx B, Mazzone M, Zacchigna S, Loges S, Pattarini L, *et al.* Anti-PlGF inhibits growth of VEGF(R)-inhibitor-resistant tumors without affecting healthy vessels. Cell. 2007; 131(3):463-75.

[4] Guo T, Hajdu M, Agaram NP, Shinoda H, Veach D, Clarkson BD, *et al.* Mechanisms of sunitinib resistance in gastrointestinal stromal tumors harboring KITAY502-3ins mutation: an *in vitro* mutagenesis screen for drug resistance. Clinical cancer research. 2009; 15(22):6862-70.

[5] Paez-Ribes M, Allen E, Hudock J, Takeda T, Okuyama H, Vinals F, *et al.* Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Cancer cell. 2009; 15(3):220-31.

[6] von Bubnoff N, Engh RA, Aberg E, Sanger J, Peschel C, Duyster J. FMS-like tyrosine kinase 3-internal tandem duplication tyrosine kinase inhibitors display a nonoverlapping profile of resistance mutations *in vitro*. Cancer research. 2009; 69(7):3032-41.

[7] Bhatt RS, Wang X, Zhang L, Collins MP, Signoretti S, Alsop DC, *et al.* Renal cancer resistance to antiangiogenic therapy is delayed by restoration of angiostatic signaling. Molecular cancer therapeutics. 2010; 9(10):2793-802.

[8] Hammers HJ, Verheul HM, Salumbides B, Sharma R, Rudek M, Jaspers J, *et al.* Reversible epithelial to mesenchymal transition and acquired resistance to sunitinib in patients with renal cell carcinoma: evidence from a xenograft study. Molecular cancer therapeutics. 2010; 9(6):1525-35.

[9] Ko JS, Rayman P, Ireland J, Swaidani S, Li G, Bunting KD, *et al.* Direct and differential suppression of myeloid-derived suppressor cell subsets by sunitinib is compartmentally constrained. Cancer research. 2010; 70(9):3526-36.

[10] Shojaei F, Lee JH, Simmons BH, Wong A, Esparza CO, Plumlee PA, *et al.* HGF/c-Met acts as an alternative angiogenic pathway in sunitinib-resistant tumors. Cancer research. 2010; 70(24):10090-100.

[11] Tang TC, Man S, Xu P, Francia G, Hashimoto K, Emmenegger U, *et al.* Development of a resistance-like phenotype to sorafenib by human hepatocellular carcinoma cells is reversible and can be delayed by metronomic UFT chemotherapy. Neoplasia. 2010; 12(11):928-40.

[12] Allen E, Walters IB, Hanahan D. Brivanib, a dual FGF/VEGF inhibitor, is active both first and second line against mouse pancreatic neuroendocrine tumors developing adaptive/evasive resistance to VEGF inhibition. Clinical cancer research. 2011; 17(16):5299-310.

[13] Carbone C, Moccia T, Zhu C, Paradiso G, Budillon A, Chiao PJ, *et al.* Anti-VEGF treatment-resistant pancreatic cancers secrete proinflammatory factors that contribute to malignant progression by inducing an EMT cell phenotype. Clinical cancer research. 2011; 17(17):5822-32.

[14] Cascone T, Herynk MH, Xu L, Du Z, Kadara H, Nilsson MB, *et al.* Upregulated stromal EGFR and vascular remodeling in mouse xenograft models of angiogenesis inhibitor-resistant human lung adenocarcinoma. The Journal of clinical investigation. 2011; 121(4):1313-28.

[15] Fan F, Samuel S, Gaur P, Lu J, Dallas NA, Xia L, *et al.* Chronic exposure of colorectal cancer cells to bevacizumab promotes compensatory pathways that mediate tumour cell migration. British journal of cancer. 2011; 104(8):1270-7.

[16] Finke J, Ko J, Rini B, Rayman P, Ireland J, Cohen P. MDSC as a mechanism of tumor escape from sunitinib mediated anti-angiogenic therapy. International immunopharmacology. 2011; 11(7):856-61.

[17] Gotink KJ, Broxterman HJ, Labots M, de Haas RR, Dekker H, Honeywell RJ, *et al.* Lysosomal sequestration of sunitinib: a novel mechanism of drug resistance. Clinical cancer research. 2011; 17(23):7337-46.

[18] Karam JA, Zhang XY, Tamboli P, Margulis V, Wang H, Abel EJ, *et al.* Development and characterization of clinically relevant tumor models from patients with renal cell carcinoma. European urology. 2011; 59(4):619-28.

[19] Kutikov A, Makhov P, Golovine K, Canter DJ, Sirohi M, Street R, *et al.* Interleukin-6: a potential biomarker of resistance to multitargeted receptor tyrosine kinase inhibitors in castration-resistant prostate cancer. Urology. 2011; 78(4):968.e7-11.

[20] Li JL, Sainson RC, Oon CE, Turley H, Leek R, Sheldon H, *et al.* DLL4-Notch signaling mediates tumor resistance to anti-VEGF therapy *in vivo*. Cancer research. 2011; 71(18):6073-83.

[21] Morgillo F, Cascone T, D'Aiuto E, Martinelli E, Troiani T, Saintigny P, *et al.* Antitumour efficacy of MEK inhibitors in human lung cancer cells and their derivatives with acquired resistance to different tyrosine kinase inhibitors. British journal of cancer. 2011; 105(3):382-92.

[22] van Zijl F, Mall S, Machat G, Pirker C, Zeillinger R, Weinhaeusel A, *et al.* A human model of epithelial to mesenchymal transition to monitor drug efficacy in hepatocellular carcinoma progression. Molecular cancer therapeutics. 2011; 10(5):850-60.

[23] Zhang L, Bhasin M, Schor-Bardach R, Wang X, Collins MP, Panka D, *et al.* Resistance of renal cell carcinoma to sorafenib is mediated by potentially reversible gene expression. PloS one. 2011; 6(4):e19144.

[24] Bender C, Ullrich A. PRKX, TTBK2 and RSK4 expression causes Sunitinib resistance in kidney carcinoma- and melanoma-cell lines. International journal of cancer Journal international du cancer. 2012; 131(2):E45-55.

[25] Blivet-Van Eggelpoel MJ, Chettouh H, Fartoux L, Aoudjehane L, Barbu V, Rey C, *et al.* Epidermal growth factor receptor and HER-3 restrict cell response to sorafenib in hepatocellular carcinoma cells. Journal of hepatology. 2012; 57(1):108-15.

[26] Gulhati P, Zaytseva YY, Valentino JD, Stevens PD, Kim JT, Sasazuki T, *et al.* Sorafenib enhances the therapeutic efficacy of rapamycin in colorectal cancers harboring oncogenic KRAS and PIK3CA. Carcinogenesis. 2012; 33(9):1782-90.

[27] Hu YL, DeLay M, Jahangiri A, Molinaro AM, Rose SD, Carbonell WS, *et al.* Hypoxia-induced autophagy promotes tumor cell survival and adaptation to antiangiogenic treatment in glioblastoma. Cancer research. 2012; 72(7):1773-83.

[28] Kharaziha P, Rodriguez P, Li Q, Rundqvist H, Bjorklund AC, Augsten M, *et al.* Targeting of distinct signaling cascades and cancer-associated fibroblasts define the efficacy of Sorafenib against prostate cancer cells. Cell death & disease. 2012; 3:e262.

[29] Maione F, Capano S, Regano D, Zentilin L, Giacca M, Casanovas O, *et al.* Semaphorin 3A overcomes cancer hypoxia and metastatic dissemination induced by antiangiogenic treatment in mice. The Journal of clinical investigation. 2012; 122(5):1832-48.

[30] Makhov PB, Golovine K, Kutikov A, Teper E, Canter DJ, Simhan J, *et al.* Modulation of Akt/mTOR signaling overcomes sunitinib resistance in renal and prostate cancer cells. Molecular cancer therapeutics. 2012; 11(7):1510-7.

[31] Miyake M, Anai S, Fujimoto K, Ohnishi S, Kuwada M, Nakai Y, *et al.* 5-fluorouracil enhances the antitumor effect of sorafenib and sunitinib in a xenograft model of human renal cell carcinoma. Oncology letters. 2012; 3(6):1195-202.

[32] Moore AS, Faisal A, Gonzalez de Castro D, Bavetsias V, Sun C, Atrash B, *et al.* Selective FLT3 inhibition of FLT3-ITD+ acute myeloid leukaemia resulting in secondary D835Y mutation: a model for emerging clinical resistance patterns. Leukemia. 2012; 26(7):1462-70.

[33] Shan J, Shen J, Liu L, Xia F, Xu C, Duan G, *et al.* Nanog regulates self-renewal of cancer stem cells through the insulin-like growth factor pathway in human hepatocellular carcinoma. Hepatology. 2012; 56(3):1004-14.

[34] Shojaei F, Simmons BH, Lee JH, Lappin PB, Christensen JG. HGF/c-Met pathway is one of the mediators of sunitinib-induced tumor cell type-dependent metastasis. Cancer letters. 2012; 320(1):48-55.

[35] Tai WT, Cheng AL, Shiau CW, Liu CY, Ko CH, Lin MW, *et al.* Dovitinib induces apoptosis and overcomes sorafenib resistance in hepatocellular carcinoma through SHP-1-mediated inhibition of STAT3. Molecular cancer therapeutics. 2012; 11(2):452-63.

[36] Zhou Q, Lv H, Mazloom AR, Xu H, Ma'ayan A, Gallo JM. Activation of alternate prosurvival pathways accounts for acquired sunitinib resistance in U87MG glioma xenografts. The Journal of pharmacology and experimental therapeutics. 2012; 343(2):509-19.

[37] Baker SD, Zimmerman EI, Wang YD, Orwick S, Zatechka DS, Buaboonnam J, *et al.* Emergence of polyclonal FLT3 tyrosine kinase domain mutations during sequential therapy with sorafenib and sunitinib in FLT3-ITD-positive acute myeloid leukemia. Clinical cancer research. 2013; 19(20):5758-68.

[38] Burbridge MF, Bossard CJ, Saunier C, Fejes I, Bruno A, Leonce S, *et al.* S49076 is a novel kinase inhibitor of MET, AXL, and FGFR with strong preclinical activity alone and in association with bevacizumab. Molecular cancer therapeutics. 2013; 12(9):1749-62.

[39] Carbonell WS, DeLay M, Jahangiri A, Park CC, Aghi MK. beta1 integrin targeting potentiates antiangiogenic therapy and inhibits the growth of bevacizumab-resistant glioblastoma. Cancer research. 2013; 73(10):3145-54.

[40] Chow AK, Ng L, Lam CS, Wong SK, Wan TM, Cheng NS, *et al.* The Enhanced metastatic potential of hepatocellular carcinoma (HCC) cells with sorafenib resistance. PloS one. 2013; 8(11):e78675.

[41] Chung AS, Wu X, Zhuang G, Ngu H, Kasman I, Zhang J, *et al.* An interleukin-17-mediated paracrine network promotes tumor resistance to anti-angiogenic therapy. Nature medicine. 2013; 19(9):1114-23.

[42] Gassenmaier M, Chen D, Buchner A, Henkel L, Schiemann M, Mack B, *et al.* CXC chemokine receptor 4 is essential for maintenance of renal cell carcinoma-initiating cells and predicts metastasis. Stem cells. 2013; 31(8):1467-76.

[43] Giovannini C, Baglioni M, Baron Toaldo M, Ventrucci C, D'Adamo S, Cipone M, *et al.* Notch3 inhibition enhances sorafenib cytotoxic efficacy by promoting GSK3b phosphorylation and p21 down-regulation in hepatocellular carcinoma. Oncotarget. 2013; 4(10):1618-31.

[44] Gyanchandani R, Sano D, Ortega Alves MV, Klein JD, Knapick BA, Oh S, *et al.* Interleukin-8 as a modulator of response to bevacizumab in preclinical models of head and neck squamous cell carcinoma. Oral oncology. 2013; 49(8):761-70.

[45] Heffeter P, Atil B, Kryeziu K, Groza D, Koellensperger G, Korner W, *et al.* The ruthenium compound KP1339 potentiates the anticancer activity of sorafenib *in vitro* and *in vivo*. European journal of cancer. 2013; 49(15):3366-75.

[46] Ho JY, Hsu RJ, Wu CL, Chang WL, Cha TL, Yu DS, *et al.* Ovatodiolide Targets beta -Catenin Signaling in Suppressing Tumorigenesis and Overcoming Drug Resistance in Renal Cell Carcinoma. Evidence-based complementary and alternative medicine : eCAM. 2013; 2013:161628.

[47] Hsueh YS, Lin CL, Chiang NJ, Yen CC, Li CF, Shan YS, *et al.* Selecting tyrosine kinase inhibitors for gastrointestinal stromal tumor with secondary KIT activation-loop domain mutations. PloS one. 2013; 8(6):e65762.

[48] Huang XY, Ke AW, Shi GM, Zhang X, Zhang C, Shi YH, *et al.* alphaB-crystallin complexes with 14-3-3zeta to induce epithelial-mesenchymal transition and resistance to sorafenib in hepatocellular carcinoma. Hepatology. 2013; 57(6):2235-47.
[49] Jahangiri A, De Lay M, Miller LM, Carbonell WS, Hu YL, Lu K, *et al.* Gene expression profile identifies tyrosine kinase c-Met as a targetable mediator of antiangiogenic therapy resistance. Clinical cancer research. 2013; 19(7):1773-83.
[50] Karashima T, Fukuhara H, Tamura K, Ashida S, Kamada M, Inoue K, *et al.* Expression of angiogenesis-related gene profiles and development of resistance to tyrosine-kinase inhibitor in advanced renal cell carcinoma: characterization of sorafenib-resistant cells derived from a cutaneous metastasis. International journal of urology : official journal of the Japanese Urological Association. 2013; 20(9):923-30.
[51] Kumar K, Wigfield S, Gee HE, Devlin CM, Singleton D, Li JL, *et al.* Dichloroacetate reverses the hypoxic adaptation to bevacizumab and enhances its antitumor effects in mouse xenografts. Journal of molecular medicine. 2013; 91(6):749-58.
[52] Liang Y, Zheng T, Song R, Wang J, Yin D, Wang L, *et al.* Hypoxia-mediated sorafenib resistance can be overcome by EF24 through Von Hippel-Lindau tumor suppressor-dependent HIF-1alpha inhibition in hepatocellular carcinoma. Hepatology. 2013; 57(5):1847-57.
[53] Ou DL, Lee BS, Chang YC, Lin LI, Liou JY, Hsu C, *et al.* Potentiating the efficacy of molecular targeted therapy for hepatocellular carcinoma by inhibiting the insulin-like growth factor pathway. PloS one. 2013; 8(6):e66589.
[54] Panka DJ, Liu Q, Geissler AK, Mier JW. Effects of HDM2 antagonism on sunitinib resistance, p53 activation, SDF-1 induction, and tumor infiltration by CD11b+/Gr-1+ myeloid derived suppressor cells. Molecular cancer. 2013; 12:17.
[55] Phan VT, Wu X, Cheng JH, Sheng RX, Chung AS, Zhuang G, *et al.* Oncogenic RAS pathway activation promotes resistance to anti-VEGF therapy through G-CSF-induced neutrophil recruitment. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110(15):6079-84.
[56] Piao Y, Liang J, Holmes L, Henry V, Sulman E, de Groot JF. Acquired resistance to anti-VEGF therapy in glioblastoma is associated with a mesenchymal transition. Clinical cancer research. 2013; 19(16):4392-403.
[57] Rosa R, Damiano V, Nappi L, Formisano L, Massari F, Scarpa A, *et al.* Angiogenic and signalling proteins correlate with sensitivity to sequential treatment in renal cell cancer. British journal of cancer. 2013; 109(3):686-93.
[58] Sakai I, Miyake H, Fujisawa M. Acquired resistance to sunitinib in human renal cell carcinoma cells is mediated by constitutive activation of signal transduction pathways associated with tumour cell proliferation. BJU international. 2013; 112(2):E211-20.
[59] Shen YC, Ou DL, Hsu C, Lin KL, Chang CY, Lin CY, *et al.* Activating oxidative phosphorylation by a pyruvate dehydrogenase kinase inhibitor overcomes sorafenib resistance of hepatocellular carcinoma. British journal of cancer. 2013; 108(1):72-81.
[60] Su SC, Hu X, Kenney PA, Merrill MM, Babaian KN, Zhang XY, *et al.* Autotaxin-lysophosphatidic acid signaling axis mediates tumorigenesis and development of acquired resistance to sunitinib in renal cell carcinoma. Clinical cancer research. 2013; 19(23):6461-72.
[61] van Malenstein H, Dekervel J, Verslype C, Van Cutsem E, Windmolders P, Nevens F, *et al.* Long-term exposure to sorafenib of liver cancer cells induces resistance with epithelial-to-mesenchymal transition, increased invasion and risk of rebound growth. Cancer letters. 2013; 329(1):74-83.
[62] Wehler TC, Hamdi S, Maderer A, Graf C, Gockel I, Schmidtmann I, *et al.* Single-agent therapy with sorafenib or 5-FU is equally effective in human colorectal cancer xenograft--no benefit of combination therapy. International journal of colorectal disease. 2013; 28(3):385-98.
[63] Williams AB, Nguyen B, Li L, Brown P, Levis M, Leahy D, *et al.* Mutations of FLT3/ITD confer resistance to multiple tyrosine kinase inhibitors. Leukemia. 2013; 27(1):48-55.
[64] Xia H, Ooi LL, Hui KM. MicroRNA-216a/217-induced epithelial-mesenchymal transition targets PTEN and SMAD7 to promote drug resistance and recurrence of liver cancer. Hepatology. 2013; 58(2):629-41.
[65] Xin HW, Ambe CM, Hari DM, Wiegand GW, Miller TC, Chen JQ, *et al.* Label-retaining liver cancer cells are relatively resistant to sorafenib. Gut. 2013; 62(12):1777-86.
[66] Xu J, Wang J, Xu B, Ge H, Zhou X, Fang JY. Colorectal cancer cells refractory to anti-VEGF treatment are vulnerable to glycolytic blockade due to persistent impairment of mitochondria. Molecular cancer therapeutics. 2013; 12(5):717-24.
[67] Bae JS, Noh SJ, Kim KM, Jang KY, Chung MJ, Kim DG, *et al.* Serum response factor induces epithelial to mesenchymal transition with resistance to sorafenib in hepatocellular carcinoma. International journal of oncology. 2014; 44(1):129-36.
[68] Croci DO, Cerliani JP, Dalotto-Moreno T, Mendez-Huergo SP, Mascanfroni ID, Dergan-Dylon S, *et al.* Glycosylation-dependent lectin-receptor interactions preserve angiogenesis in anti-VEGF refractory tumors. Cell. 2014; 156(4):744-58.
[69] D'Amato C, Rosa R, Marciano R, D'Amato V, Formisano L, Nappi L, *et al.* Inhibition of Hedgehog signalling by NVP-LDE225 (Erismodegib) interferes with growth and invasion of human renal cell carcinoma cells. British journal of cancer. 2014; 111(6):1168-79.
[70] Fernandez-Fuente G, Mollinedo P, Grande L, Vazquez-Barquero A, Fernandez-Luna JL. Culture dimensionality influences the resistance of glioblastoma stem-like cells to multikinase inhibitors. Molecular cancer therapeutics. 2014; 13(6):1664-72.
[71] Gao H, Deng L. Sphingosine kinase-1 activation causes acquired resistance against Sunitinib in renal cell carcinoma cells. Cell biochemistry and biophysics. 2014; 68(2):419-25.
[72] Gotink KJ, Broxterman HJ, Honeywell RJ, Dekker H, de Haas RR, Miles KM, *et al.* Acquired tumor cell resistance to sunitinib causes resistance in a HT-29 human colon cancer xenograft mouse model without affecting sunitinib biodistribution or the tumor microvasculature. Oncoscience. 2014; 1(12):844-53.
[73] Guerrouahen BS, Pasquier J, Kaoud NA, Maleki M, Beauchamp MC, Yasmeen A, *et al.* Akt-activated endothelium constitutes the niche for residual disease and resistance to bevacizumab in ovarian cancer. Molecular cancer therapeutics. 2014; 13(12):3123-36.
[74] Harada K, Miyake H, Kusuda Y, Fujisawa M. Characterization of mechanism involved in acquired resistance to sorafenib in a mouse renal cell cancer RenCa model. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2014; 16(9):801-6.
[75] Huang L, Hu C, Di Benedetto M, Varin R, Liu J, Wang L, *et al.* Induction of multiple drug resistance in HMEC-1 endothelial cells after long-term exposure to sunitinib. OncoTargets and therapy. 2014; 7:2249-55.
[76] Isham CR, Netzel BC, Bossou AR, Milosevic D, Cradic KW, Grebe SK, *et al.* Development and characterization of a differentiated thyroid cancer cell line resistant to VEGFR-targeted kinase inhibitors. The Journal of clinical endocrinology and metabolism. 2014; 99(6):E936-43.
[77] Li D, Xie K, Ding G, Li J, Chen K, Li H, *et al.* Tumor resistance to anti-VEGF therapy through up-regulation of VEGF-C expression. Cancer letters. 2014; 346(1):45-52.
[78] Liang J, Piao Y, Holmes L, Fuller GN, Henry V, Tiao N, *et al.* Neutrophils promote the malignant glioma phenotype through S100A4. Clinical cancer research. 2014; 20(1):187-98.
[79] Mesange P, Poindessous V, Sabbah M, Escargueil AE, de Gramont A, Larsen AK. Intrinsic bevacizumab resistance is associated with prolonged activation of autocrine VEGF signaling and hypoxia tolerance in colorectal cancer cells and can be overcome by nintedanib, a small molecule angiokinase inhibitor. Oncotarget. 2014; 5(13):4709-21.
[80] Nam SW, Park KC, Yang KJ, Lee B, Kim SW. Genetic screen identifies suppressor of morphogenesis in genitalia-1 (SMG-1) as a modulator of sorafenib resistance in hepatocellular carcinoma cell lines. International journal of oncology. 2014; 45(4):1450-6.
[81] Nam SW, Park KC, Choi HS, Lee B, Kim SW. Identification of Zinc Finger, MYM-type 2 (ZMYM2) as a regulator of sorafenib resistance in hepatocellular carcinoma cell lines. J Gastroenterol Hepatol. 2014; 29(3):633-9.
[82] Nguyen TV, Sleiman M, Moriarty T, Herrick WG, Peyton SR. Sorafenib resistance and JNK signaling in carcinoma during extracellular matrix stiffening. Biomaterials. 2014; 35(22):5749-59.

[83] Prior C, Perez-Gracia JL, Garcia-Donas J, Rodriguez-Antona C, Guruceaga E, Esteban E, *et al.* Identification of tissue microRNAs predictive of sunitinib activity in patients with metastatic renal cell carcinoma. PloS one. 2014; 9(1):e86263.
[84] Rigamonti N, Kadioglu E, Keklikoglou I, Wyser Rmili C, Leow CC, De Palma M. Role of angiopoietin-2 in adaptive tumor resistance to VEGF signaling blockade. Cell reports. 2014; 8(3):696-706.
[85] Rudalska R, Dauch D, Longerich T, McJunkin K, Wuestefeld T, Kang TW, *et al. In vivo* RNAi screening identifies a mechanism of sorafenib resistance in liver cancer. Nature medicine. 2014; 20(10):1138-46.
[86] Su JC, Tseng PH, Wu SH, Hsu CY, Tai WT, Li YS, *et al.* SC-2001 overcomes STAT3-mediated sorafenib resistance through RFX-1/SHP-1 activation in hepatocellular carcinoma. Neoplasia. 2014; 16(7):595-605.
[87] Xu H, Zhao L, Fang Q, Sun J, Zhang S, Zhan C, *et al.* MiR-338-3p inhibits hepatocarcinoma cells and sensitizes these cells to sorafenib by targeting hypoxia-induced factor 1alpha. PloS one. 2014; 9(12):e115565.
[88] Zhai B, Hu F, Jiang X, Xu J, Zhao D, Liu B, *et al.* Inhibition of Akt reverses the acquired resistance to sorafenib by switching protective autophagy to autophagic cell death in hepatocellular carcinoma. Molecular cancer therapeutics. 2014; 13(6):1589-98.
[89] Zhang W, Gao C, Konopleva M, Chen Y, Jacamo RO, Borthakur G, *et al.* Reversal of acquired drug resistance in FLT3-mutated acute myeloid leukemia cells *via* distinct drug combination strategies. Clinical cancer research. 2014; 20(9):2363-74.
[90] Zhao D, Zhai B, He C, Tan G, Jiang X, Pan S, *et al.* Upregulation of HIF-2alpha induced by sorafenib contributes to the resistance by activating the TGF-alpha/EGFR pathway in hepatocellular carcinoma cells. Cellular signalling. 2014; 26(5):1030-9.
[91] Adelaiye R, Ciamporcero E, Miles KM, Sotomayor P, Bard J, Tsompana M, *et al.* Sunitinib dose escalation overcomes transient resistance in clear cell renal cell carcinoma and is associated with epigenetic modifications. Molecular cancer therapeutics. 2015; 14(2):513-22.
[92] Ciamporcero E, Miles KM, Adelaiye R, Ramakrishnan S, Shen L, Ku S, *et al.* Combination strategy targeting VEGF and HGF/c-met in human renal cell carcinoma models. Molecular cancer therapeutics. 2015; 14(1):101-10.
[93] Curtarello M, Zulato E, Nardo G, Valtorta S, Guzzo G, Rossi E, *et al.* VEGF-targeted therapy stably modulates the glycolytic phenotype of tumor cells. Cancer research. 2015; 75(1):120-33.
[94] Fernando J, Malfettone A, Cepeda EB, Vilarrasa-Blasi R, Bertran E, Raimondi G, *et al.* A mesenchymal-like phenotype and expression of CD44 predict lack of apoptotic response to sorafenib in liver tumor cells. International journal of cancer Journal international du cancer. 2015; 136(4):E161-72.
[95] Huang L, Hu C, M DIB, Varin R, Liu J, Jin J, *et al.* Cross-drug resistance to sunitinib induced by doxorubicin in endothelial cells. Oncology letters. 2015; 9(3):1287-92.
[96] Jedeszko C, Paez-Ribes M, Di Desidero T, Man S, Lee CR, Xu P, *et al.* Postsurgical adjuvant or metastatic renal cell carcinoma therapy models reveal potent antitumor activity of metronomic oral topotecan with pazopanib. Science translational medicine. 2015; 7(282):282ra50.
[97] Kuczynski EA, Lee CR, Man S, Chen E, Kerbel RS. Effects of Sorafenib Dose on Acquired Reversible Resistance and Toxicity in Hepatocellular Carcinoma. Cancer research. 2015; 75(12):2510-9.
[98] Lin H, Jiang X, Zhu H, Jiang W, Dong X, Qiao H, *et al.* 2ME2 inhibits the activated hypoxia-inducible pathways by cabozantinib and enhances its efficacy against medullary thyroid carcinoma. Tumour Biol. 2015.
[99] Liu Y, Ye X, Zhang JB, Ouyang H, Shen Z, Wu Y, *et al.* PROX1 promotes hepatocellular carcinoma proliferation and sorafenib resistance by enhancing beta-catenin expression and nuclear translocation. Oncogene. 2015; 34(44):5524-35.
[100] Lo J, Lau EY, Ching RH, Cheng BY, Ma MK, Ng IO, *et al.* Nuclear factor kappa B-mediated CD47 up-regulation promotes sorafenib resistance and its blockade synergizes the effect of sorafenib in hepatocellular carcinoma in mice. Hepatology. 2015; 62(2):534-45.
[101] Metzelder SK, Michel C, von Bonin M, Rehberger M, Hessmann E, Inselmann S, *et al.* NFATc1 as a therapeutic target in FLT3-ITD-positive AML. Leukemia. 2015; 29(7):1470-7.
[102] Ou DL, Shyue SK, Lin LI, Feng ZR, Liou JY, Fan HH, *et al.* Growth arrest DNA damage-inducible gene 45 gamma expression as a prognostic and predictive biomarker in hepatocellular carcinoma. Oncotarget. 2015; 6(29):27953-65.
[103] Sasano T, Mabuchi S, Kuroda H, Kawano M, Matsumoto Y, Takahashi R, *et al.* Preclinical Efficacy for AKT Targeting in Clear Cell Carcinoma of the Ovary. Molecular cancer research : MCR. 2015; 13(4):795-806.
[104] Schnegg CI, Yang MH, Ghosh SK, Hsu MY. Induction of Vasculogenic Mimicry Overrides VEGF-A Silencing and Enriches Stem-like Cancer Cells in Melanoma. Cancer research. 2015; 75(8):1682-90.
[105] Shibasaki N, Yamasaki T, Kanno T, Arakaki R, Sakamoto H, Utsunomiya N, *et al.* Role of IL13RA2 in Sunitinib Resistance in Clear Cell Renal Cell Carcinoma. PloS one. 2015; 10(6):e0130980.
[106] Varna M, Gapihan G, Feugeas JP, Ratajczak P, Tan S, Ferreira I, *et al.* Stem cells increase in numbers in perinecrotic areas in human renal cancer. Clinical cancer research. 2015; 21(4):916-24.
[107] Yamada T, Abei M, Danjoh I, Shirota R, Yamashita T, Hyodo I, *et al.* Identification of a unique hepatocellular carcinoma line, Li-7, with CD13(+) cancer stem cells hierarchy and population change upon its differentiation during culture and effects of sorafenib. BMC cancer. 2015; 15:260.
[108] Yeh CC, Hsu CH, Shao YY, Ho WC, Tsai MH, Feng WC, *et al.* Integrated Stable Isotope Labeling by Amino Acids in Cell Culture (SILAC) and Isobaric Tags for Relative and Absolute Quantitation (iTRAQ) Quantitative Proteomic Analysis Identifies Galectin-1 as a Potential Biomarker for Predicting Sorafenib Resistance in Liver Cancer. Molecular & cellular proteomics : MCP. 2015; 14(6):1527-45.
[109] Zhu Y, Liu H, Xu L, An H, Liu W, Liu Y, *et al.* p21-activated kinase 1 determines stem-like phenotype and sunitinib resistance *via* NF-kappaB/IL-6 activation in renal cell carcinoma. Cell death & disease. 2015; 6:e1637.