Supplementary Table 2 | *In vitro* mechanistic studies of possible modes of action of statins			
Study	**Statin**	**Major findings**	**Effect reversed by**
Multiple cancer cell lines			
Keyomarsi *et al.* (1991)[1]	Lovastatin	Synchronization of normal and tumour cells reversibly in the G_1 phase of the cell cycle	Mevalonic acid
Spampanato *et al.* (2012)[2]	Simvastatin	Induction of apoptosis features only in cancer cells. Overexpression of *BAX* and inhibition of *BCL2*	–
Malenda *et al.* (2012)[3]	Atorvastatin, cerivastatin, fluvastatin, lovastatin, simvastatin	Decrease in glucose analogue uptake in tumour cells	Mevalonic acid, FPP, cholesterol
Menter *et al.* (2011)[4]	Pravastatin, simvastatin	Simvastatin inhibited growth of most tumour cell lines more effectively than pravastatin. Poorly differentiated cancer cells more responsive than well-differentiated cancer cells. Alterations in mitochondrial networks, changes in cellular morphology related to cofilin regulation and loss of p-caveolin. Redistribution of solute carrier organic anion transporter family member 1B1 and HMG-CoA reductase to perinuclear sites.	–
Nübel *et al.* (2004)[5]	Lovastatin, simvastatin	Inhibition of TNF-α induced- E-selectin expression, and cell adhesion and invasion	GGPP
Endothelial cancer cell lines			
Vincent *et al.* (2001)[6]	Cerivastatin	Inhibition of angiogenesis, due to decrease in endothelial cell locomotion, mainly related to delocalization of transforming protein RhoA from cell membrane to cytoplasm. Decrease in MMP-2 secretion.	GGPP; MMP-2 decrease reversed by FPP
Breast cancer cell lines			
Addeo *et al.* (1996)[7]	Lovastatin, simvastatin	DNA synthesis reduced by >90% in normal and transformed cells.	17β-estradiol (in oestrogen-receptor positive cells)
Sánchez *et al.* (2008)[8]	Fluvastatin, simvastatin, atorvastatin	Antiproliferation, decrease in DNA synthesis, cell-cycle arrest in G_1 and G_2/M. Fluvastatin caused loss in mitochondrial membrane potential. Increase in ROS production.	Antioxidant N-acetyl-cysteine abrogated ROS increase
Kang *et al.* (2009)[9]	Lovastatin, simvastatin	Decreased isoprenylated HRAS in membrane fraction. Inhibited HRAS-induced invasion. Down regulated MMP-9, MMP-2. Inactivated HRAS downstream signalling molecules.	Inhibited invasion reversed by FPP
Klawitter *et al.* (2010)[10]	Lovastatin	Inhibition of proliferation. In proteomic profiling: decreased expression of active RAS. Modulation of E2F1 pathway through regulation of expression of prohibitin and Rb, leading to changes in MCM7 and MSH2. Regulation of AKT signalling pathway. Metabolomics: suppression of glycolitic and Krebs cycle activity, and lipid biosynthesis.	–
Lung cancer cell lines			
Maksimova *et al.* (2008)[11]	Lovastatin	Increase in apoptosis and necrosis in 3 of 4 cell lines. Reduced cell survival with increase in cell-cycle check-point inhibitors $p21^{WAF}$ and/or $p27^{KIP}$, and decrease in cyclin D1. Decreased glutathione. Increased cytochrome C release and increased activated caspase-3.	–
Pelaia *et al.* (2012)[12]	Simvastatin	Reduced ERK phosphorylation, induction of apoptosis.	–
Chen *et al.* (2012)[13]	Atorvastatin	VEGF expression inhibition via ROS production inhibition, through suppression of Rac1/NAPDH oxidase activity, and upregulation of glutathione peroxidase and catalase activity.	–
Colorectal cancer cell lines			
Agarwal *et al.* (1999)[14]	Lovastatin	Increased apoptosis induced by 5-FU or cisplatin. Decreased expression of the antiapoptotic protein BCL2, increased expression of the proapoptotic protein BAX.	GGPP
Notarnicola *et al.* (2004)[15]	Simvastatin	Antiproliferative and proapoptotic effects in one cell line, cell growth inhibition and no apoptosis in another cell line.	–
Kodach *et al.* (2007) and	Lovastatin	Differing sensitivities of different cell lines. In sensitive cell lines: induction of BMP2 levels by causing BMP2 promoter	Noggin (specific inhibitor of

(2011)[16,17]		demethylation, activation of BMP pathway, induction of BMP target gene *ID2*. Altering gene expression causing a shift from a stem-like state to a more-differentiated state.	BMPs). *SMAD4* knockout.
Oesophageal cancer cell lines			
Sadaria *et al.* (2011)[18]	Simvastatin, atorvastatin, pravastatin	Simvastatin caused decreased cell viability and proliferation, increased apoptosis, and attenuation of ICAM-1 expression and NF-κB activation. Atorvastatin had mild effects and pravastatin had no effect.	–
Pancreatic cancer cell lines			
Kusama *et al.* (2001)[19]	Lovastatin fluvastatin	Attenuated EGF-induced membrane translocation of transforming protein RhoA, and inhibited EGF-induced cancer cell invasion.	All-*trans* geranylgeraniol
Cholangiocarcinoma cell lines			
Miller *et al.* (2011)[20]	Simvastatin	Reduction in cell viability and apoptosis. RAC1/lipid rafts co-localization and RAC1 activity reduction.	Mevalonate, FPP, GGPP (partial blockade). Cholesterol.
Kamigaki *et al.* (2011)[21]	Atorvastatin, pitavastatin	Suppressed cell proliferation. Sub-G_1 fraction increase. Increased caspase-3 level, ERK reduction. Additive proliferation suppression with statin pretreatment compared with chemotherapy alone.	–
Liver cancer cell lines			
Relja *et al.* (2010)[22]	Simvastatin	Cell growth reduction, apoptosis induction, impaired cell-cycle progression, inhibition of CDKs and cyclins, enhanced CDK inhibitors p19, p27	–
Kah *et al.* (2012)[23]	Multiple	Fluvastatin, simvastatin, lovastatin caused cell viability reduction and apoptosis induction, only in hepatoma cells and not in normal hepatocytes—only after *TP53* knockdown in *TP53* overexpressed cell line.	Mevalonate, GGPP
Renal cancer cell lines			
Woodard *et al.* (2008)[24]	Fluvastatin	Apoptosis induction, proliferation suppression via inhibition of AKT/mTOR pathway.	–
Bladder cancer cell lines			
Jakóbisiak *et al.* (1991)[25]	Lovastatin	G_1 arrest. Reduction in proliferation-associated nuclear proteins Ki-67 and p105 expression. Dissociation of p21ras from the cell membrane translocation toward the cytoplasm	Mevalonate
Ovarian cancer cell lines			
Martirosyan *et al.* (2010)[26]	Lovastatin	Apoptosis induction in a p53-independent manner. Doxorubicin synergism by blocking doxorubicin efflux from cells.	Mevalonate, FPP, GGPP
Thyroid cancer cell lines			
Laezza *et al.* (2008)[27]	Lovastatin	RAS activation blockade through farnesylation inhibition. Apoptosis induction. Increased ROS levels through ERK1/2 signalling inhibition and Mn-SOD expression.	Antioxidant pyrrolidine dithiocarbamate, SOD-mimetic
Zeybek *et al.* (2011)[28]	Rosuvastatin	Decreased cell viability, G_1 phase arrest. Caspase-3 activity and apoptotic index increase.	–
Zhong *et al.* (2011)[29]	Lovastatin	G_0/G_1 arrest. Inhibited proliferation. Rho geranylgeranylation reduction, p27 and CDK4 increase. Cyclin A2, cyclin D3, Rb protein level decrease. Increased CDK2-p27 complex formation, CDK2 activity decrease.	p27 antisense oligonucleotide, mevalonate, GGPP (partially)
Shui *et al.* (2012)[30]	Lovastatin	Thyroid differentiation. Impact on proteins involved in protein folding, biomolecule metabolism, signal transduction, protein expression and protein degradation.	–
Osteosarcoma cell lines			
Fromigué *et al.* (2008)[31]	Atorvastatin	Reduced cell migration and invasion, GGPP-dependent, independent of apoptosis induction. Reduced MMP-2, MMP-9, MMP-14, TIMP2 expression via inhibited JNK.	MMP-2, MMP-14, JNK, mevalonate, GGPP, RhoA
Neuroblastoma cell lines			
Dimitroulakos *et al.* (1996)[32]	Lovastatin	Cytotoxicity restricted to drug-resistant P-glycoprotein-expressing neuroblastoma. Potentiated by dibutyryl cyclic AMP.	–

Glioblastoma cell lines			
Bouterfa *et al.* (2000)[33]	Lovastatin	Block in RAS-mediated signalling. Reduced proliferation, apoptosis induction	Mevalonate
Yanae *et al.* (2011)[34]	Mevastatin, fluvastatin, simvastatin	Cell proliferation inhibition, apoptosis induction. Caspase-3 activity increase. Decreased extracellular ERK1/2 and Akt.	GGPP
Abbreviations: 5-FU, 5-fluorouracil; BMP, bone morphogenic protein; CDK, cyclin dependent kinase; FPP, farnesyl pyrophosphate; GGPP, geranylgeranylpyrophosphate; MMP, matrix metalloproteinase; ROS, reactive oxygen species.			

1. Keyomarsi, K., Sandoval, L., Band, V. & Pardee, A. B. Synchronization of tumor and normal cells from G1 to multiple cell cycles by lovastatin. *Cancer Res.* **51**, 3602–3609 (1991).
2. Spampanato, C. *et al.* Simvastatin inhibits cancer cell growth by inducing apoptosis correlated to activation of Bax and down-regulation of BCL-2 gene expression. *Int. J. Oncol.* **40**, 935–941 (2012).
3. Malenda, A. *et al.* Statins impair glucose uptake in tumor cells. *Neoplasia* **14**, 4 (2012).
4. Menter, D. G. *et al.* Differential effects of pravastatin and simvastatin on the growth of tumor cells from different organ sites. *PLoS ONE* **6**, e28813 (2011).
5. Nübel, T., Dippold, W., Kleinert, H., Kaina, B. & Fritz, G. Lovastatin inhibits Rho-regulated expression of E-selectin by TNFalpha and attenuates tumor cell adhesion. *FASEB J.* **18**, 140–142 (2004).
6. Vincent, L. *et al.* Inhibition of endothelial cell migration by cerivastatin, an HMG-CoA reductase inhibitor: contribution to its anti-angiogenic effect. *FEBS Lett.* **495**, 159–166 (2001).
7. Addeo, R. *et al.* Stimulation of human breast cancer MCF-7 cells with estrogen prevents cell cycle arrest by HMG-CoA reductase inhibitors. *Biochem Biophys Res Commun.* **220**, 864–870 (1996).
8. Sánchez, C. A. *et al.* Statin-induced inhibition of MCF-7 breast cancer cell proliferation is related to cell cycle arrest and apoptotic and necrotic cell death mediated by an enhanced oxidative stress. *Cancer Invest.* **26**, 698–707 (2008).
9. Kang, S., Kim, E. S. & Moon, A. Simvastatin and lovastatin inhibit breast cell invasion induced by H-Ras. *Oncol. Rep.* **21**, 1317–1322 (2009).
10. Klawitter, J., Shokati, T., Moll, V., Christians, U. & Klawitter, J. Effects of lovastatin on breast cancer cells: a proteo-metabonomic study. *Breast Cancer Res.* **12**, R16 (2010).
11. Maksimova, E., Yie, T. A. &, Rom WN. *In vitro* mechanisms of lovastatin on lung cancer cell lines as a potential chemopreventive agent. *Lung* **186**, 45–54 (2008).
12. Pelaia, G. *et al.* Effects of statins and farnesyl transferase inhibitors on ERK phosphorylation, apoptosis and cell viability in non-small lung cancer cells. *Cell Prolif.* **45**, 557–565 (2012).
13. Chen, J. *et al.* Atorvastatin reduces vascular endothelial growth factor (VEGF) expression in human non-small cell lung carcinomas (NSCLCs) via inhibition of reactive oxygen species (ROS) production. *Mol Oncol.* **6**, 62–72 (2012).
14. Agarwal, B. *et al.* Lovastatin augments apoptosis induced by chemotherapeutic agents in colon cancer cells. *Clin. Cancer Res.* **5**, 2223–2229 (1999).
15. Notarnicola, M. *et al.* Up-regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in left-sided human colon cancer. *Anticancer Res.* **24**, 3837–3842 (2004).
16. Kodach, L. L. *et al.* The effect of statins in colorectal cancer is mediated through the bone morphogenetic protein pathway. *Gastroenterology* **133**, 1272–1281 (2007).
17. Kodach, L. L. *et al.* Statins augment the chemosensitivity of colorectal cancer cells inducing epigenetic reprogramming and reducing colorectal cancer cell 'stemness' via the bone morphogenetic protein pathway. *Gut* **60**, 1544–1553 (2011).
18. Sadaria, M. R. *et al.* Statin therapy attenuates growth and malignant potential of human esophageal adenocarcinoma cells. *J. Thorac. Cardiovasc. Surg.* **142**, 1152–1160 (2011).
19. Kusama, T. *et al.* Inhibition of epidermal growth factor-induced RhoA translocation and invasion of human pancreatic cancer cells by 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibitors. *Cancer Res.* **61**, 4885–4891 (2001).
20. Miller, T. *et al.* Simvastatin stimulates apoptosis in cholangiocarcinoma by inhibition of Rac1 activity. *Dig. Liver Dis.* **43**, 395–403 (2011).
21. Kamigaki, M. *et al.* Statins induce apoptosis and inhibit proliferation in cholangiocarcinoma cells. *Int. J. Oncol.* **39**, 561–568 (2011).
22. Relja, B. *et al.* Simvastatin inhibits cell growth and induces apoptosis and G0/G1 cell cycle arrest in hepatic cancer cells. *Int. J. Mol. Med.* **26**, 735–741 (2010).
23. Kah, J. *et al.* Selective induction of apoptosis by HMG-CoA reductase inhibitors in hepatoma cells and dependence on p53 expression. *Oncol. Rep.* **28**, 1077–1083 (2012).
24. Woodard, J., Sassano, A., Hay, N. & Platanias, L. C. Statin-dependent suppression of the Akt/mammalian target of rapamycin signaling cascade and programmed cell death 4 up-regulation in renal cell carcinoma. *Clin Cancer Res.* **14**, 4640–4649 (2008).

25. Jakóbisiak, M., Bruno, S., Skierski, J. S. & Darzynkiewicz, Z. Cell cycle-specific effects of lovastatin. *Proc. Natl Acad. Sci. USA* **88**, 3628–3632 (1991).
26. Martirosyan, A., Clendening, J. W., Goard, C. A. & Penn, L. Z. Lovastatin induces apoptosis of ovarian cancer cells and synergizes with doxorubicin: potential therapeutic relevance. *BMC Cancer* **10**, 103 (2010).
27. Laezza, C. *et al.* Lovastatin induces apoptosis of k-ras-transformed thyroid cells via inhibition of ras farnesylation and by modulating redox state. *J. Mol. Med. (Berl.)* 86, :1341–1351 (2008).
28. Zeybek, N. D. *et al.* Rosuvastatin induces apoptosis in cultured human papillary thyroid cancer cells. *J. Endocrinol.* **210**, 105–115 (2011).
29. Zhong, W. B. *et al.* Lovastatin inhibits proliferation of anaplastic thyroid cancer cells through up-regulation of p27 by interfering with the Rho/ROCK-mediated pathway. *Biochem. Pharmacol.* **82**, 1663–1672 (2011).
30. Shui, H. A., Hsia, C. W., Chen, H. M., Chang, T. C. & Wang, C. Y. Proteomics and bioinformatics analysis of lovastatin-induced differentiation in ARO cells. *J. Proteomics* **75**, 1170–1180 (2012).
31. Fromigué, O., Hamidouche, Z. & Marie, P. J. Blockade of the RhoA-JNK-c-Jun-MMP2 cascade by atorvastatin reduces osteosarcoma cell invasion. *J. Biol. Chem.* **283**, 30549–30556 (2008).
32. Dimitroulakos, J. & Yeger, H. HMG-CoA reductase mediates the biological effects of retinoic acid on human neuroblastoma cells: lovastatin specifically targets P-glycoprotein-expressing cells. *Nat. Med.* **2**, 326–333 (1996).
33. Bouterfa, H. L. *et al.* Inhibition of Ras farnesylation by lovastatin leads to downregulation of proliferation and migration in primary cultured human glioblastoma cells. *Anticancer Res.* **20**, 2761–2771 (2000).
34. Yanae, M. *et al.* Statin-induced apoptosis via the suppression of ERK1/2 and Akt activation by inhibition of the geranylgeranyl-pyrophosphate biosynthesis in glioblastoma. *J. Exp. Clin. Cancer Res.* **30**, 74 (2011).