## The authors' reply

## Robert Dorsam and J. Silvio Gutkind

Oral and Pharyngeal Cancer Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, Maryland 20892–4330, USA. Correspondence to J.S.G. e-mail: <u>sg39v@nih.gov</u>

We thank Ben-Shlomo and Melmed for their comments concerning the role of adrenocorticotropin hormone (ACTH) and thyrotropin secreting hormone (TSH) receptors in pituitary cancer. We may owe some clarification, as we did not intend to implicate the ACTH and TSH receptors as causing pituitary cancer through a mechanism that acts on endogenous pituitary gland receptors. Indeed, we have not stated this in the text of the review, nor does table 1 specify this. Pituitary tumours are characterized by the hyper-secretion of TSH and ACTH, resulting in systemic complications in the target organs of these hormones, the thyroid and adrenal glands. Given this information, we included these receptors in the pituitary section of table 1 on the basis that a characteristic of this cancer is the over-production of ACTH and TSH, which bind to their cognate G-protein-coupled receptors (GPCRs) in their target organs. This is well reviewed in the provided reference<sup>1</sup> (reference 147 in the article). Our earlier version(s) of the text were more descriptive of this topic, but space limitations did not permit an in-depth treatment of this particular subject in the final version. Thus, table 1 was left with the receptors listed, and a reference to a review on the topic.

On the other hand, we agree on the role of TSH receptors and their mutations in thyroid tumours, which we believe was well described in the text (Page 87, first column, second paragraph) and in table 1, in agreement with Ben-Shlomo's and Melmed's comments. We did not describe these mutations in the context of pituitary tumours. Neither we nor the text of the review is at odds with the statements of Ben-Shlomo and Melmed, and we feel that a clarification is most practical.

Table 1 has been modified to reflect this point and is shown below.

We would like to thank Ben-Shlomo and Melmed for bringing this to our attention.

1. Kaltsas, G. A. & Grossman, A. B. Malignant pituitary tumours. *Pituitary* **1**, 69–81 (1998).

CancerReceptorLigandProcessSelected referencesBread cancerP/R1ThrombinGrowth metastais angiogenesis12.12.133Bread cancerE/2; IP4PGE2Growth metastais angiogenesis42.44.134CACR4SDF1Metastasis: angiogenesis70GrowthOestrogenGrowth? Informane therapy resistance?23-26Colon cancerE/2; IP4PGE2Growth30-34IP4IPAGrowth126Ert cerctorsEndothelin1Survival41PRA1ThrombinGrowth metastais angiogenesis136Art AllThrombinGrowth metastais angiogenesis136ProceptorsPGE2Growth metastais: angiogenesis136ProceptorsPGE2Growth: angiogenesis: metastais46GRPRGRPGrowth3.16.17.139Male-RNeurometinBGrowth: metastais: angiogenesis136Small-cell lung concerGRPRGRPGrowth: metastais416CCK, CCK,CCKGrowth: metastais416CCK, CCK,CCKGrowth: metastais416Non-small-cell lung concerGRPRGRPGrowth: metastaisCCR2US.GROGrowth: metastais416CCK2SDF1Growth: metastais416CCK2SDF1Growth: metastais416ConcerCCK4SDF1Migration: metastaisCCR2GROGrowth: metastais416ConcerCCK4SDF1 </th <th colspan="6">Table 1   GPCRs in cancer</th>	Table 1   GPCRs in cancer					
EP2:EP4PGE2Growth; metastasis; angiogenesis42,41,134CXCR4SDF1Metastasis; angiogenesis70GP30OestrogenGrowth? Hornore-therappresistance?23-56Colon cancerEP2,EP4PGE2Growth; metastasis; angiogenesis30-34HPALPAGrowthGrowth126PRAIhrombinGrowth; metastasis; angiogenesis31-34PRANorsGrowth; metastasis; angiogenesis31-34PRANorsGrowth; metastasis; angiogenesis31-36PRASDF1Metastasis31-36PRAGRPGrowth; metastasis; angiogenesis31-36PRASDF1Metastasis31-37Small-cell lung cancerGRPRGRPGrowth; metastasis; angiogenesis31-31Non-small-cell lung cancerGRPRGCA2Growth; metastasis; angiogenesis31-31Non-small-cell lung cancerGRPRGCA2Growth; metastasi; angiogenesis31-31Non-small-cell lung cancerGRPRGRPAGrowth31-31QCA2GROA2Growth; metastasi; angiogenesis31-31QCA2GROA2 </th <th>Cancer</th> <th>Receptor</th> <th>Ligand</th> <th>Process</th> <th>Selected references</th>	Cancer	Receptor	Ligand	Process	Selected references	
CXCR4SDF1Metastasis angiogenesis70Colon cancerEPR30OestrogenGrowth'Hormon-therapy resistance?23-26Colon cancerEPR4POE2Growth, metastasis: angiogenesis30-34EPR4POE2Growth, metastasis: angiogenesis30-34ErrocciptorsEndothelin-1Survival41PAR1ThrombinGrowth; migration3135FrizzledsWntsGrowth; migration3136CR74SDF1Metastasis316ErrocciptorsPOE2Growth; metastasis; angiogenesis313ErrocciptorsPOE2Growth; majoigenesis; metastasis46GRRGRPGrowth; angiogenesis; metastasis46GRRGRPGrowth; survival318Small-cell lang cancerMRRGRPGrowth; metastasis; angiogenesis31617.139Non-small-cell lang cancerCCK2CCKGrowth; metastasis410Non-small-cell langPreceptorsPOE2Growth; metastasis410Non-small-cell langEP receptorsPOE2Growth; metastasis412CCK, CCK4SDF1Growth; metastasis414414Ovarian cancerCCR2GROaGrowth; metastasis413CCR2GROaGrowth; metastasis414414Ovarian cancerCCR2CACKGrowth414Prestate cancerGRPGRPGrowth; metastasis416Pitulary cancerTSHGrowth; metastasis416414 </td <td rowspan="4">Breast cancer</td> <td>PAR1</td> <td>Thrombin</td> <td>Growth; metastasis; angiogenesis</td> <td>12,132,133</td>	Breast cancer	PAR1	Thrombin	Growth; metastasis; angiogenesis	12,132,133	
CPR30CestrogenGrowth? Hormon-therapy resistance?23-26Colon cancerFP2, EP4PCE2Growth; restatasis; angiogenesis30-34LPALPAGrowthCord126FreeeptorsEndothelin-1Survival41PAR1TrombinGrowth; migration135FritzledsWritsGrowth; migration135FritzledsWritsGrowth; migration137EPreceptorsPCE2Growth; migration136CXCR4SDF1Metastasis137EPreceptorsPCE2Growth; migration138PAR1ThrombinMetastasis136Small-celllung cancerGRPRGRPGrowth; survival316,17,39Non-small-cellCCK, CCK,CCKGrowth; survival31Non-small-cell lung cancerCCK, CCK,CCKGrowth; metastasis140Non-small-cell lung cancerPPR-ceptorsPCE2Growth; metastasis141CACR4SDF1Growth; metastasis; angiogenesis141ConcerCCK, CCK,CCKGrowth; metastasis; angiogenesis141Paretaproid gland cancerRPRGROGrowth; angiogenesis141Prostate cancerGRPRGROGrowth; angiogenesis141Prostate cancerGRPAGROGrowth; angiogenesis141Prostate cancerFI, CCK, CCKGrowth; angiogenesis141Prostate cancerFI, CLTHGrowthGrowth; metastasi; angiogenesis141 </td <td>EP2; EP4</td> <td>PGE2</td> <td>Growth; metastasis; angiogenesis</td> <td>42,44,134</td>		EP2; EP4	PGE2	Growth; metastasis; angiogenesis	42,44,134	
Colon cancerFP2, FP4PGE2Growth; metastasis; angiogenesis30-34LPA,LPA,Growth126ErreceptorsEndothelin-1Survival41PR4ThrombinGrowth; migration135FrizzledsWntsGrowth; migration62Head and neck cancerCXCR2U.B. GR0xGrowth; migration62GRPACRPGrowth; angiogenesis; metastasis; angiogenesis136GRPAGRPGrowth; angiogenesis; metastasis46GRPAGRPGrowth; angiogenesis; metastasis46CRPAGRPGrowth; angiogenesis; metastasis137PreceptorsPGE2Growth; angiogenesis; metastasis138Small-celllung cancerGRPRGRPGrowth31617139NMB-RNeuromedin BGrowth; metastasis; angiogenesis45141CCK; CCK,CCKGrowth; metastasis; angiogenesis45141CancerCXCR4SDF1Migration; metastasis; angiogenesis45142CXCR4SDF1Migration; metastasis; angiogenesis413GrowthGrowth; metastasis; angiogenesis413CACR1SDF1Migration; metastasis; angiogenesis414CACR2GRPAGROwGrowth; metastasis; angiogenesis415CACR2GROaGrowth; metastasis; angiogenesis413CACR4SDF1Migration; metastasis; angiogenesis414CACR4SDF1Migration; metastasis; angiogenesis414CACR2GROa <td< td=""><td>CXCR4</td><td>SDF1</td><td>Metastasis; angiogenesis</td><td>70</td></td<>		CXCR4	SDF1	Metastasis; angiogenesis	70	
Image: Part of the part o		GPR30	Oestrogen	Growth? Hormone-therapy resistance?	23–26	
FraceptorsEndothelin-1Survival41PAR1ThrombinGrowth; migration135FrizzledsWntsGrowth; migration135FrizzledsWntsGrowth; mistatsis; angiogenesis136CXCR4LB; GR0 $\alpha$ Growth; mistatsis; angiogenesis; metastasis137EP receptorsPGE2Growth; mistatsis; angiogenesis; metastasis46GRPGRPGrowth; survival138Small-cell lung cancerGRPRGRPGrowth; survival31CK2; CCK2CCKGrowth3,16,17,139NMB-RNeuromedin BGrowth; survival31CK2; CCK2CCKGrowth; survival31CKR4SDF1Growth; metastasis; angiogenesis445,141CKR4SDF1Growth; metastasis; angiogenesis445,141CACR4SDF1Growth; metastasis; angiogenesis445,141CXCR4SDF1Growth; metastasis; angiogenesis445,141CXCR4SDF1Growth; metastasis; angiogenesis143jlAR; jBZARNNKGrowth?144Ovarian cancerIPA, LPA,LPAGrowth; metastasis; angiogenesis415CXCR2GRPGrowthGrowth145partityroid gland cancerCASRCalciamGrowth; metastasis; angiogenesis141Prathyroid gland cancerCASRCalciamGrowth; metastasis148Prathyroid gland cancerCASRCalciamGrowth; metastasis1418Prathyroid gland cancer <t< td=""><td rowspan="5">Colon cancer</td><td>EP2, EP4</td><td>PGE2</td><td>Growth; metastasis; angiogenesis</td><td>30–34</td></t<>	Colon cancer	EP2, EP4	PGE2	Growth; metastasis; angiogenesis	30–34	
PAR1ThrombinGrowth; migration138FrizzledsWntsGrowth62Head and neck cancerCXCR2IL8; GRO $\alpha$ Growth; metastasis; angiogenesis136EP receptorsPGE2Growth; metastasi; angiogenesis; metastasis46GRRGRPGrowth; surival138PAR1ThrombinMetastasis135Small-celllung cancerGRRGRPGrowth; surival316MNB-RNeuromedin BGrowth3,16,17,139Non-small-celllungEP receptorsPGE2Growth; metastasis; angiogenesis416CXCR4SDF1Growth; metastasis; angiogenesis451416CXCR4SDF1Growth; metastasis; angiogenesis451,411CXCR4SDF1Migration; metastasis; angiogenesis451,411CXCR4SDF1Migration; metastasis; angiogenesis416CXCR4SDF1Migration; metastasis; angiogenesis413CXCR4SDF1Migration; metastasis; angiogenesis414CXCR4SDF1Migration; metastasis; angiogenesis415CXCR4SDF1Migration; metastasis; angiogenesis415CXCR4SDF1Migration; metastasis; angiogenesis415CXCR4SDF1Migration; metastasis; angiogenesis416PixterCXCR4GRO $\alpha$ Growth; metastasis; angiogenesis115Pancreatic cancerGRPGRO $\alpha$ Growth; metastasis; angiogenesis116PixterCXCR4CXCR4GRO $\alpha$ Gr		LPA <sub>1</sub>	LPA	Growth	126	
FrizzledsWntsGrowth62Head and neck cancerCXCR2LB; GRO $\alpha$ Growth; metastasis; angiogenesis136CXCR4SDF1Metastasis137EPreceptorsPGE2Growth; angiogenesis; metastasis46GRPRGRPGROwth; surival138PAR1ThrombinMetastasis; angiogenesis13Small-cell lung cancerGRPRGRPGrowth; surival3.16.17CXCR4SDF1Growth; surival3CXCR4SDF1Growth; metastasis140Non-small-cell lungEP receptorsPGE2Growth; metastasisCXCR4SDF1Growth; metastasis141CXCR4SDF1Growth; metastasis141CXCR4SDF1Migration; metastasis141CXCR4SDF1Migration; metastasis141Ovarian cancerLPA, LPA,LPAGrowth; metastasis141Ovarian cancerGRPRGROGrowth141Paretypoid gland cancerGRPRGROGrowth141Prostate cancerGRPRGRPGrowth141Prostate cancerGRPRGROGrowth141Prostate cancerGRPRGROGrowth141Prostate cancerGRPRGROGrowth141Prostate cancerGRPRGROGrowth141Prostate cancerGRPRGROGrowth141Prostate cancerGRRGROGrowth141 <td< td=""><td>ET receptors</td><td>Endothelin-1</td><td>Survival</td><td>41</td></td<>		ET receptors	Endothelin-1	Survival	41	
Head and neck cancerCKCR2LB; GRQαGrowth; metastasis; angiogenesis136CKCR4SDF1Metastasis137FP receptorsPGE2Growth; survival138GRPRGRPGrowth; survival138Small-cell lung cancerGRPRCRPGrowth3,16,17,139CK, iCCK,CCKGrowth; survival3,16,17CCK, iCCK,CCKGrowth; metastasis140Non-small-cell lungEP receptorsPGE2Growth; metastasis141CCR4SDF1Growth; metastasis141CACR4SDF1Growth; metastasis141CACR4SDF1Misration; metastasis141CACR4SDF1Misration; metastasis141CACR4SDF1Misration; metastasis; angiogenesis45,141CACR4SDF1Misration; metastasis; angiogenesis1412CACR4SDF1Misration; metastasis; angiogenesis1413Malk Rig DARNNKGrowth?144Ovarian cancerCRRCRPGrowth; metastasi; angiogenesis4,151CACR2CROCROwth; metastasi; angiogenesis1416Pitutiary cancerCASRCalciumGrowth; metastasi; angiogenesis14,161Pitutiary cancerTSH receptor*TSH*Growth; invivial; metastasis14,163Pitutiary cancerFQ, EPAGrowth; invivial; metastasis14,163Pitutiary cancerTSH receptor*CH*Growth; invivial; metastasis14,163Pitut		PAR1	Thrombin	Growth; migration	135	
CXCR4SD 1MetastasisMetastasisMetastasisEP receptorsPGE2Growth; angiogenesis; metastasis46GRPRGRPGrowth; survival138PAR1ThrombinMetastasis; angiogenesis13Small-cell lung cancerGRPRGRPGrowth3.16.17.13CCK; ICCK,CCKGrowth; survival3.16.17.13CCK; ICCK,CCKGrowth; survival3.16.17.13CCK; ICCK,CCKGrowth; survival3.16.17.13CCK; ICCK,CCKGrowth; survival3.16.17.13CancerEP receptorsPGE2Growth; survival3.16.17.13CancerCCCR2IL8; GRO $\alpha$ Growth; metastasis; angiogenesis142CACR4SDF1Migration; metastasis; angiogenesis142CACR4SDF1Migration; metastasis; angiogenesis143GarcerGRPAGRO $\alpha$ Growth; metastasis; angiogenesis141Qvarian cancerCKR2GRO $\alpha$ Growth; angiogenesis15Parcetic cancerGRPRGRPGrowth3.16.17.13Parathyroid gland cancerCASRCalciumGrowth; survival51.147Prostate cancerPAR1ThrombinGrowth; survival; metastasis; angiogenesis14.89Prostate cancerPAR1AcTHPGrowth; survival; metastasis; angiogenesis27IPA,LPAGrowth; survival; metastasis; angiogenesis14.89Prostate cancerPAR1Hodotelin11Growth; survival; metastasis; angiogenesi		Frizzleds	Wnts	Growth	62	
FP receptorsPGE2Growth; angiogenesis; metastasis46GRPRGRPGrowth; survival138PAR1ThrombinMetastasis; angiogenesis13Small-cell lung cancerGRPRGRPGrowth3.16.17CCK; CCKCCKGrowth; survival31CCK; CCKCCKGrowth; survival31CCK; CCKCCKGrowth; survival31CCK; CCKCCKGrowth; metastasis; angiogenesis440Non-small-cell lungPreceptorsPGE2Growth; metastasis; angiogenesis4141CancerCCR4SDF1Migration; metastasis; angiogenesis4142Ovarian cancerPA_LPA,LPAGrowth; metastasis; angiogenesis4143Ovarian cancerPA_LPA,LPAGrowth; metastasis; angiogenesis415CCK2GROQGrowth; metastasis; angiogenesis415Parcettic cancerRPRGRQGrowth; metastasis; angiogenesis415Parcettic cancerCASRCalciumGrowth146Pituitary cancerTSH receptor*TSH*Growth147Prostate cancerRPRCalciumGrowth147Prostate cancerFL2, PAPGE2Growth; metastasis; angiogenesis414Pituitary cancerGRPRCalciumGrowth; survival; metastasis1418Pituitary cancerGASRCalciumGrowth148Pituitary cancerGRPRGalciumGrowth1418Pituitary cancerGASR <td rowspan="5">Head and neck cancer</td> <td>CXCR2</td> <td>IL8; GROα</td> <td>Growth; metastasis; angiogenesis</td> <td>136</td>	Head and neck cancer	CXCR2	IL8; GROα	Growth; metastasis; angiogenesis	136	
RPR PAR1GRP ThrombinGrowth; survival138Small-cell lung cancer CCK; CCK2GRPR GRPRGrowth3.16.17.39Small-cell lung cancer CCK; CCK2GRPRGrowth3.16.17.39NMB-R CCK4Neuromedin BGrowth; survival3CCK; CCK2CCKGrowth; survival3CCK4SDF1Growth; metastasis140Non-small-cell lung CancerEP receptorsPGE2Growth; metastasis; angiogenesis45.141CACR4SDF1Migration; metastasis; angiogenesis142CACR4SDF1Migration; metastasis; angiogenesis143j1AR; j2ARNNKGrowth; metastasis; angiogenesis143Ovarian cancerGRPRGRO $\alpha$ Growth; metastasis; angiogenesis145Parchytorid gland cancerGRPRGRO $\alpha$ Growth; metastasis; angiogenesis145Prathyroid gland cancerCASRCalciumGrowth; angiogenesis141Protytic dataTSH*Growth; angiogenesis141Protytic dataCASRCalciumGrowth; angiogenesis141Protytic dataCASRCalciumGrowth; angiogenesis141Prostate cancerFACalciumGrowth; invasion144Prostate cancerFAEndothelin 1Growth; invasion144FIFIGrowth; invasion144141Prostate cancerFAEndothelin 1Growth; invasion144B182BradykininGrowth; invasion144		CXCR4	SDF1	Metastasis	137	
PAR1ThrombinMetastasis; angiogenesis13Small-cell lung cancer AMB-RGRPRGRPGrowth3.16.17.139NMB-RNeuromedin BGrowth; survival3.16.17.139CK, 2CCK_CCKGrowth; survival3.16.17CKR4SDF1Growth; metastasis; angiogenesis45.141CancerEP receptorsPGE2Growth; metastasis; angiogenesis45.141CACR4SDF1Migration; metastasis; angiogenesis45.141CACR4SDF1Migration; metastasis; angiogenesis45.141CACR4SDF1Migration; metastasis; angiogenesis45.141CACR4SDF1Migration; metastasis; angiogenesis45.141Ovarian cancerEP receptorsGROGrowth; metastasis; angiogenesis45.141Ovarian cancerCACR2GROGrowth; metastasis; angiogenesis45.141Parethyroid gland cancerGRPRGROGrowth; angiogenesis45.141Prathyroid gland cancerCASRCACR4Growth316.17.139Prathyroid gland cancerGRPRCalciumGrowth; survival14.141Protate cancerFARCACH4Growth14.141Protate cancerPAR1ThrombinGrowth; invasion14.81F1_AAngiotensin IIGrowth; invasion14.81F1_AAngiotensin IIGrowth; invasion14.81F1_APACGRPAGrowth; invasion14.141F1_AAngiotensin IIGrowth; invasion14.141 <tr< td=""><td>EP receptors</td><td>PGE2</td><td>Growth; angiogenesis; metastasis</td><td>46</td></tr<>		EP receptors	PGE2	Growth; angiogenesis; metastasis	46	
$ \begin{aligned} & \text{Small-cell lung cancer} \\ & \text{Small-cell lung cancer} \\ & \text{SMB-R} \\ & \text{NMB-R} \\ & \text{Neuromedin B} \\ & \text{Growth} \\ & \text{Growth: survival} \\ & \text{Growth: survival} \\ & \text{CK}, \text{GCK} \\ & \text{CCK} \\ & \text{CCK} \\ & \text{SDF1} \\ & \text{Growth: metastasis; angiogenesis} \\ & \text{45,141} \\ & \text{CACR4} \\ & \text{SDF1} \\ & \text{Crowth: metastasis; angiogenesis} \\ & \text{45,141} \\ & \text{Growth: metastasis; angiogenesis} \\ & \text{45,141} \\ & \text{Growth: metastasis; angiogenesis} \\ & \text{45,141} \\ & \text{Growth: metastasis; angiogenesis} \\ & \text{4142} \\ & \text{CACR4} \\ & \text{SDF1} \\ & \text{Migrior: metastasis; angiogenesis} \\ & \text{142} \\ & \text{CACR4} \\ & \text{SDF1} \\ & \text{Migrior: metastasis; angiogenesis} \\ & \text{143} \\ & \text{g1AR; g2AR} \\ & \text{NNK} \\ & \text{Growth? metastasis; angiogenesis} \\ & \text{4.15} \\ & \text{CACR2} \\ & \text{GRO} \\ & \text{Growth: metastasis; angiogenesis} \\ & \text{4.15} \\ & \text{CACR2} \\ & \text{GRO} \\ & \text{Growth: metastasis; angiogenesis} \\ & \text{4.15} \\ & \text{CACR2} \\ & \text{GRO} \\ & \text{Growth: metastasis; angiogenesis} \\ & \text{4.15} \\ & \text{CACR2} \\ & \text{GRO} \\ & \text{Growth: metastasis; angiogenesis} \\ & \text{4.15} \\ & \text{CACR2} \\ & \text{GRO} \\ & \text{Growth: metastasis; angiogenesis} \\ & \text{4.15} \\ & \text{CACR2} \\ & \text{CACR} \\ & \text{Growth} \\ & \text{Growth: metastasis; angiogenesis} \\ & \text{4.16} \\ & \text{Pituitary cancer} \\ & \text{CASR} \\ & \text{Calcium} \\ & \text{Growth} \\ & \text{Growth} \\ & \text{4.16} \\ & \text{F1}_{A} \\ & \text{CACR4} \\ & \text{F1}_{A} \\ & \text{ACTH}^{H} \\ & \text{Growth: survival} \\ & \text{f1}_{A} \\ & \text{ACTH}^{H} \\ & \text{Growth: metastasis; angiogenesis} \\ & \text{4.16} \\ & \text{F2}_{A} \\ & \text{E1} \\ & \text{CACR2} \\ & \text{E1} \\ & \text{B1,B2} \\ & \text{B1} \\ & \text{CACR2} \\ & \text{LPA} \\ & \text{CACR4} \\ & CA$		GRPR	GRP	Growth; survival	138	
NMB-RNeuromedin BGrowth3.16.17CCK, CCK,CCKGrowth; survival3CXCR4SDF1Growth; metastasis140Non-small-cell lung cancerEP receptorsPGE2Growth; metastasis; angiogenesis45.141CXCR4SDF1Migration; metastasis; angiogenesis142CXCR4SDF1Migration; metastasis; angiogenesis143Mark, BZARNNKGrowth; metastasis; angiogenesis143Ovarian cancerCRACRO $\alpha$ Growth; metastasis; angiogenesis115Pancreatic cancerGRPRGRPGrowth; angiogenesis15Parceatic cancerCASRCalciumGrowth146Pituitary cancerTSH receptor*TSH*Growth; survival31,147Prostate cancerFACalciumGrowth; isurvival51,147Prostate cancerEF_ACACH*Growth; isurvival51,147Prostate cancerEF_AEndothelin 1Growth; isurvival51,147Prostate cancerEF_AEndothelin 1Growth; isurvival; metastasis148Prostate cancerEF_AEndothelin 1Growth; isurvival; metastasis141RB, B2BradykininGrowth; invasion14,19144GRPRGRPGrowth; invasion14,19141RB, B2BradykininGrowth; invasion14,19144B1,B2BradykininGrowth; invasion14,19144MelanomaGRPRGRPAGrowth; metastasi; angioge		PAR1	Thrombin	Metastasis; angiogenesis	13	
CCK, CCK, CCKCCKGrowth; survival3CXCR4SDF1Growth; metastasis140Non-small-cell lung cancerEP receptorsPGE2Growth; metastasis; angiogenesis45.141CXCR4SDF1Migration; metastasis; angiogenesis142CXCR4SDF1Migration; metastasis; angiogenesis143j1AR; β2ARNNKGrowth; metastasis; angiogenesis143Ovarian cancerCKCR2CROαGrowth; metastasis; angiogenesis145Pancreatic cancerGRPRGRPGrowth; metastasis; angiogenesis155Pancreatic cancerGRPRCCKGrowth146Pituitary cancerTSH receptor*CSKGrowth147Prostate cancerFSH receptor*TSH*Growth; survival51,147ACTHR*ACTH*Growth; survival51,147ACTHR*ACTH*Growth; survival148Prostate cancerFGErdothelin1Growth; survival148FIErdothelin1Growth; survival; metastasis148AT1AngiotensinIIGrowth; survival; metastasis141B1,82BradykininGrowth; survival; invasion141MelanomaGRPRGRPGrowth; invasion141MelanomaKL8; GROαGrowth; metastasi; angiogenesis27FgIR3BradykininGrowth; invasion141Basal-cell carcinomaMC1RKSHSensitivity to UV-induced DNA damage50.149Basal-cell carcinoma <td rowspan="4">Small-cell lung cancer</td> <td>GRPR</td> <td>GRP</td> <td>Growth</td> <td>3,16,17,139</td>	Small-cell lung cancer	GRPR	GRP	Growth	3,16,17,139	
CXCR4SDF1Growth; metastasis140Non-small-celllung cancerEP receptorsPGE2Growth; metastasis; angiogenesis45,141CXCR2IL8; GRO $\alpha$ Growth; metastasis; angiogenesis142CXCR4SDF1Migration; metastasis; angiogenesis143 $\beta_{1AR}$ ; $\beta_{2AR}$ NNKGrowth?144Ovarian cancerLPA_LPA_LPAGrowth?144Ovarian cancerCRCR2GRO $\alpha$ Growth; metastasis; angiogenesis4.15CXCR2GRO $\alpha$ Growth; metastasis; angiogenesis145Pancreatic cancerGRPRGRPGrowth145Parathyroid gland cancerCAS;CCKGrowth3Parathyroid gland cancerTSH receptor*TSH*Growth147Prostate cancerTSH receptor*TSH*Growth148P1uitary cancerTSH receptor*TSH*Growth148ET_AEndothelin 1Growth; survival; metastasis; angiogenesis141Prostate cancerPAR1ThrombinGrowth; invasion148ET_AEndothelin 1Growth; invasion148EP2_EP4PGE2Growth; metastasis; angiogenesis27LPA,LPAGrowth; survival; invasion141B1,B2BradykininGrowth; survival; invasion141MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149ETs_basal-cell		NMB-R	Neuromedin B	Growth	3,16,17	
Non-small-cell lung cancerFP receptorsPGE2Growth; metastasis; angiogenesis45,141CXCR2IL8; GRO $\alpha$ Growth; metastasis; angiogenesis142CXCR4SDF1Migration; metastasis; angiogenesis143 $\beta$ 1AR; $\beta$ 2ARNNKGrowth?144Ovarian cancerLPA,-LPA,LPAGrowth?144CXCR2GRO $\alpha$ Growth; metastasis; angiogenesis4,15CXCR2GRO $\alpha$ Growth; metastasis; angiogenesis163Pancreatic cancerGRPRGRPGrowth145CCK; CCK,CCKGrowth3Parathyroid gland cancerCASRCalciumGrowth; survival146Pituitary cancerTSH receptor*TSH*Growth; survival147Prostate cancerPAR1ThrombinGrowth; survival; metastasis14,18AT1Angiotensin IIGrowth; unvision14,89FJ2, EP4PGE2Growth; invasion14,19PAIPAGRO $\alpha$ Growth; unvision14,19MelanomaMC1RMSHGrowth; unvival; invasion14,19MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149Rasal-cell carcinomaSmoothenedSonic hedgehogGrowth; metastasis; angiogenesis151Basal-cell carcinomaSmoothenedSonic hedgehogGrowth; metastasis; angiogenesis151Basal-cell carcinomaSmoothenedSonic hedgehogGrowth; metastasis; angiogenesis151Basal-cell carcinoma <td>CCK<sub>1</sub>; CCK<sub>2</sub></td> <td>ССК</td> <td>Growth; survival</td> <td>3</td>		CCK <sub>1</sub> ; CCK <sub>2</sub>	ССК	Growth; survival	3	
		CXCR4	SDF1	Growth; metastasis	140	
$\begin{tabular}{ c c c c } \hline RCR2 & IL8; GR0 & Growth; metastasis; angiogenesis & 142 \\ \hline CXCR4 & SDF1 & Migration; metastasis; angiogenesis & 143 \\ \hline \beta1AR; \beta2AR & NNK & Growth? & 144 \\ \hline Ovarian cancer & LPALPA_3 & LPA & Growth; metastasis; angiogenesis & 4.15 \\ \hline CXCR2 & GR0 & Growth; metastasis; angiogenesis & 15 \\ \hline Pancreatic cancer & GRPR & GRP & Growth & 145 \\ \hline CCK; CCK_2 & CCK & Growth & 3 \\ \hline Parathyroid gland cancer & CASR & Calcium & Growth & 146 \\ \hline Pituitary cancer & TSH receptor* & TSH* & Growth & 147 \\ \hline Prostate cancer & TSH receptor* & TSH* & Growth & 147 \\ \hline Prostate cancer & TSH receptor* & TSH* & Growth & 147 \\ \hline Prostate cancer & TATR* & ACTH* & Growth & 147 \\ \hline Prostate cancer & TATR* & Endothelin 1 & Growth; invasion & 14,89 \\ \hline ET_A & Endothelin 1 & Growth; invasion & 14,89 \\ \hline ET_A & Endothelin 1 & Growth; invasion & 14,89 \\ \hline ET_A & Endothelin 1 & Growth; invasion & 14,89 \\ \hline IPA_1 & IPA & Growth; invasion & 14,89 \\ \hline IPA_1 & IPA & Growth; invasion & 14,19 \\ \hline IPA_1 & IPA & Growth; invasion & 14,19 \\ \hline IPA_1 & IPA & Growth; invasion & 14,19 \\ \hline IPA_2 & IPA & Growth; invasion & 14,19 \\ \hline Melanoma & MC1R & MSH & Sensitivity to UV-induced DNA damage & 50,149 \\ \hline CXCR2 & IL8; GRO\alpha & Growth; metastasis; angiogenesis & 50,149 \\ \hline IPA_8 & Endothelin-1/3 & Growth & 151 \\ \hline Basal-cell carcinoma & Smoothened & Sonic hedgehog & Growth & 57,58,152 \\ \hline Testicular cancer & LH receptor & LH & Growth & 57,58,152 \\ \hline Testicular cancer & UH receptor & LH & Growth & 57,58,152 \\ \hline Testicular cancer & HH receptor & LH & Growth & 57,58,152 \\ \hline Testicular cancer & UH receptor & LH & Growth & 57,58,152 \\ \hline Testicular cancer & HH receptor & LH & Growth & 57,58,152 \\ \hline Testicular cancer & HH receptor & LH & Growth & 57,58,152 \\ \hline Testicular cancer & HH receptor & LH & Growth & 57,58,152 \\ \hline Testicular cancer & HH receptor & LH & Growth & 57,58,152 \\ \hline Testicular cancer & HH receptor & LH & Growth & 57,58,152 \\ \hline Testicular cancer & HH receptor & LH & Growth & 57,58,152 \\ \hline Testicular cancer & HH receptor &$	_	EP receptors	PGE2	Growth; metastasis; angiogenesis	45,141	
$\beta_{1}AR$ , $\beta_{2}AR$ NNKGrowth?144Ovarian cancer $LPA_{-}LPA_{3}$ LPAGrowth; metastasis; angiogenesis4.15 $CXCR2$ $CRO\alpha$ Growth; angiogenesis15Pancreatic cancerGRPRGRPGrowth145 $CCK_{1}$ , CCK,CCKGrowth3Parathyroid gland cancerCASRCalciumGrowth; survival51,147Prituitary cancerTSH receptor*TSH*Growth; survival51,147Prostate cancerPAR1ThrombinGrowth; survival148FT_AEndothelin 1Growth; survival, metastasis14,18AT1Angiotensin IIGrowth; invasion148EP2, EP4PGE2Growth; metastasis; angiogenesis27LPA,LPAGrowth; invasion14,19MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149MelanomaET <sub>a</sub> Endothelin-1/3Growth; metastasis; angiogenesis150ET <sub>a</sub> Endothelin-1/3Growth15151,147Basal-cell carcinomaSmoothenedSonic hedgehogGrowth; invasion14,19Esticular cancerLH receptorLHGrowth57,58,152Testicular cancerLH receptorLHGrowth153		CXCR2	IL8; GROα	Growth; metastasis; angiogenesis	142	
Ovarian cancerIPA_LPA_3IPAGrowth; metastasis; angiogenesis4.15Ovarian cancerGRPGRO $\alpha$ Growth; angiogenesis15Pancreatic cancerGRPRGRPGrowth145CCK; iCCK_2CCKGrowth3Parathyroid gland cancerCASRCalciumGrowth; survival51,147Pituitary cancerTSH receptor*TSH*Growth; survival51,147Prostate cancerPAR1ThrombinGrowth; invasion14,89FT_AEndothelin 1Growth; survival; metastasis14,18AT1Angiotensin IIGrowth; invasion14,89EP2, EP4PGE2Growth; invasion14,19B1,B2BradykininGrowth; invasion14,19MelanomaMC1RKSHSensitivity to UV-induced DNA damage50,149MelanomaFT <sub>a</sub> Endothelin-1/3Growth151Basal-cell carcinomaSmoothenedSonic hedgehogGrowth57,58,152Testicular cancerLH receptorLHGrowth57,58,152		CXCR4	SDF1	Migration; metastasis	143	
$\begin{tabular}{ c c c c c } \hline $\mathbf{L}$ $L$		β1AR; β2AR	NNK	Growth?	144	
$\begin{array}{llllllllllllllllllllllllllllllllllll$	Ovarian cancer	LPA <sub>1</sub> -LPA <sub>3</sub>	LPA	Growth; metastasis; angiogenesis	4,15	
CCK, iCCK, iCCKCCKCCKGrowth3Parathyroid gland cancerCASRCalciumGrowth146Pituitary cancerTSH receptor*TSH*Growth; survival51,147Prostate cancerPAR1ACTH*Growth147FT_AEndothelin 1Growth; invasion14,89ET_AEndothelin 1Growth; survival; metastasis14,18AT1Angiotensin IIGrowth; survival; metastasis14,18EP2, EP4PGE2Growth; invasion14B1,B2BradykininGrowth; invasion14,19MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149MelanomaFT_BEndothelin-1/3Growth; metastasis; angiogenesis150Basal-cell carcinomaSmoothenedSonic hedgehogGrowth151Basal-cell carcerLH receptorLHGrowthGrowth151		CXCR2	GROα	Growth; angiogenesis	15	
Parathyroid gland cancerCASRCalciumGrowth146Pituitary cancerTSH receptor*TSH*Growth; survival51,147Prostate cancerPAR1ACTH*Growth147Prostate cancerET_AEndothelin 1Growth; survival; metastasis14,89ET_AEndothelin 1Growth; survival; metastasis14,18AT1Angiotensin IIGrowth; metastasis; angiogenesis27LPA,LPAGrowth; metastasis; angiogenesis27LPA,LPAGrowth; metastasis; angiogenesis27LPA,LPAGrowth; metastasis; angiogenesis27MelanomaMC1RMSHGrowth; survival; invasion14,19MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149Basal-cell carcinomaSmoothenedSonic hedgehogGrowth; metastasi; angiogenesis151Testicular cancerLH receptorLHGrowth151	Pancreatic cancer	GRPR	GRP	Growth	145	
Pituitary cancerTSH receptor*TSH*Growth; survival51,147Private cancerPAR1ACTH*Growth147Prostate cancerPAR1ThrombinGrowth; invasion14,89 $ET_A$ Endothelin 1Growth; survival; metastasis14,18AT1Angiotensin IIGrowth; survival; metastasis14,18EP2, EP4PGE2Growth; metastasis; angiogenesis27 $LPA_1$ LPAGrowth; invasion14,19B1, B2BradykininGrowth; survival; invasion14,19MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149ET8Endothelin-1/3Growth; metastasis; angiogenesis151Basal-cell carcinomaSmoothenedSonic hedgehogGrowth151Testicular cancerLH receptorLHGrowth151		CCK <sub>1</sub> ; CCK <sub>2</sub>	ССК	Growth	3	
ACTHR*ACTH*Growth147Prostate cancerPAR1ThrombinGrowth; invasion14,89FT_AEndothelin 1Growth; survival; metastasis14,18AT1Angiotensin IIGrowth; survival; metastasis; angiogenesis27EP2, EP4PGE2Growth; metastasis; angiogenesis27IPA1LPAGrowth; invasion14B1, B2BradykininGrowth; survival; invasion14,19MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149CXCR2IL8; GROαGrowth; metastasi; angiogenesis150Endothelin-1/3GrowthGrowth; metastasi; angiogenesis151Basal-cell carcinomaSmoothenedSonic hedgehogGrowth57,58,152Testicular cancerLH receptorLHGrowth153	Parathyroid gland cancer	CASR	Calcium	Growth	146	
Prostate cancer Prostate cancerPAR1ThrombinGrowth; invasion14,89ET_AEndothelin 1Growth; survival; metastasis14,18AT1Angiotensin IIGrowth; survival; metastasis; angiogenesis148EP2, EP4PGE2Growth; metastasis; angiogenesis27LPA_1LPAGrowth; invasion14B1, B2BradykininGrowth; survival; invasion14,19GRPRGRPGrowth; metastasis; angiogenesis27MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149CXCR2IL8; GROαGrowth; metastasis; angiogenesis150ET_8Endothelin-1/3Growth151Basal-cell carcinomaSmoothenedSonic hedgehogGrowth57,58,152Testicular cancerLH receptorLHGrowth153	Pituitary cancer	TSH receptor*	TSH <sup>‡</sup>	Growth; survival	51,147	
$ \begin{array}{c c c c c } \hline FT_A & Endothelin 1 & Growth; survival; metastasis & 14,18 \\ \hline AT1 & Angiotensin II & Growth & Growth; metastasis; angiogenesis & 27 \\ \hline EP2, EP4 & PGE2 & Growth; metastasis; angiogenesis & 27 \\ \hline LPA_1 & LPA & Growth; invasion & 14 \\ \hline B1, B2 & Bradykinin & Growth; survival; invasion & 14,19 \\ \hline GRPR & GRP & GRP & Growth; migration & 14 \\ \hline Melanoma & MC1R & MSH & Sensitivity to UV-induced DNA damage & 50,149 \\ \hline CXCR2 & IL8; GRO\alpha & Growth; metastasis; angiogenesis & 150 \\ \hline ET_8 & Endothelin-1/3 & Growth & 151 \\ \hline Basal-cell carcinoma & Smoothened & Sonic hedgehog & Growth & Growth & 57,58,152 \\ \hline Testicular cancer & LH receptor & LH & Growth & Growth & 151 \\ \hline \ Delta & Conceptor & LH & Growth & Growth & 151 \\ \hline \ Delta & Conceptor & LH & Growth & Growth & 151 \\ \hline \ Delta & Conceptor & LH & Growth & Growth & 151 \\ \hline \ Delta & Conceptor & LH & Growth & Growth & 151 \\ \hline \ \ Delta & Conceptor & LH & Growth & Growth & 151 \\ \hline \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$		ACTHR <sup>†</sup>	ACTH <sup>‡</sup>	Growth	147	
AT1Angiotensin IIGrowth148FP2, EP4PGE2Growth; metastasis; angiogenesis27LPA1LPAGrowth; invasion14B1, B2BradykininGrowth; invasion14,19GRPRGRPGrowth; migration14MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149CXCR2IL8; GROαGrowth; metastasis; angiogenesis150Basal-cell carcinomaSmoothenedSonic hedgehogGrowth57,58,152Testicular cancerLH receptorLHGrowthGrowth151	Prostate cancer	PAR1	Thrombin	Growth; invasion	14,89	
EP2, EP4PGE2Growth; metastasis; angiogenesis27LPA1LPAGrowth; invasion14B1, B2BradykininGrowth; survival; invasion14,19GRPRGRPGrowth; migration14MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149CXCR2IL8; GROαGrowth; metastasis; angiogenesis150EngEndothelin-1/3Growth151Basal-cell carcinomaSmoothenedSonic hedgehogGrowth57,58,152Testicular cancerLH receptorLHGrowthGrowth151		ET <sub>A</sub>	Endothelin 1	Growth; survival; metastasis	14,18	
LPA1LPAGrowth; invasion14B1, B2BradykininGrowth; survival; invasion14,19GRPRGRPGrowth; migration14MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149CXCR2IL8; GROαGrowth; metastasis; angiogenesis150Endothelin-1/3GrowthGrowth151Basal-cell carcinomaSmoothenedSonic hedgehogGrowth57,58,152Testicular cancerLH receptorLHGrowth151		AT1	Angiotensin II	Growth	148	
B1, B2BradykininGrowth; survival; invasion14,19GRPRGRPGrowth; migration14MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149CXCR2IL8; GROαGrowth; metastasis; angiogenesis150ET <sub>B</sub> Endothelin-1/3Growth151Basal-cell carcinomaSmoothenedSonic hedgehogGrowth57,58,152Testicular cancerLH receptorLHGrowth151		EP2, EP4	PGE2	Growth; metastasis; angiogenesis	27	
GRPRGRPGrowth; migration14MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149CXCR2IL8; GROαGrowth; metastasis; angiogenesis150ETgEndothelin-1/3Growth151Basal-cell carcinomaSmoothenedSonic hedgehogGrowthTesticular cancerLH receptorLHGrowth151		LPA <sub>1</sub>	LPA	Growth; invasion	14	
MelanomaMC1RMSHSensitivity to UV-induced DNA damage50,149CXCR2IL8; GROαGrowth; metastasis; angiogenesis150ETgEndothelin-1/3Growth151Basal-cell carcinomaSmoothenedSonic hedgehogGrowthTesticular cancerLH receptorLHGrowth		B1, B2	Bradykinin	Growth; survival; invasion	14,19	
CXCR2IL8; GROαGrowth; metastasis; angiogenesis150ET_BEndothelin-1/3Growth151Basal-cell carcinomaSmoothenedSonic hedgehogGrowth57,58,152Testicular cancerLH receptorLHGrowth151		GRPR	GRP	Growth; migration	14	
ETEndothelin-1/3Growth151Basal-cell carcinomaSmoothenedSonic hedgehogGrowth57,58,152Testicular cancerLH receptorLHGrowth153	Melanoma	MC1R	MSH	Sensitivity to UV-induced DNA damage	50,149	
Basal-cell carcinomaSmoothenedSonic hedgehogGrowth57,58,152Testicular cancerLH receptorLHGrowth153		CXCR2	IL8; GROα	Growth; metastasis; angiogenesis	150	
Testicular cancer LH receptor LH Growth 153		ET <sub>B</sub>	Endothelin-1/3	Growth	151	
·	Basal-cell carcinoma	Smoothened	Sonic hedgehog	Growth	57,58,152	
Thyroid cancerTSH receptorTSHGrowth51,56	Testicular cancer	LH receptor	LH	Growth	153	
	Thyroid cancer	TSH receptor	TSH	Growth	51,56	

Many G-protein-coupled receptors (GPCRs) contribute to the aberrant growth and survival of cancer cells, as well as to tumour-induced angiogenesis and metastasis. Examples of some of the GPCRs most frequently implicated in human cancer are listed. ACTHR, adrenocorticotropic hormone receptor;  $\beta$ 1AR and  $\beta$ 2AR,  $\beta$ 1- and  $\beta$ 2adrenergic receptors; CASR, calcium sensing receptor; CCK, cholecystokinin; ETRA, endothelin receptor type A; ETRB, endothelin receptor type B; GPR30, G-proteincoupled receptor 30; GRPR, gastrin-releasing peptide receptor; IL8, interleukin 8; LH, luteinizing hormone; LPA, lysophosphatidic acid; MC1R, melanocortin 1 receptor; MSH, melanocortin 1; NMBR, neuromedin B receptor; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PGE2, prostaglandin E2; SDF1, stromal cell-derived factor 1; TSH, thyroid stimulating hormone. \*TSH acts on TSH receptor in the thyroid. \*ACTH acts on ACTHR in the adrenal glands. \*Overproduced by pituitary tumours.