EpCAM- AN OLD CANCER ANTIGEN, TURNED ONCOGENIC RECEPTOR AND ITS TARGETING IMMUNOTHERAPY

George Zhu
Institute of Oncology, Tehran University of Medical Sciences, Tehran, Iran.

ABSTRACT
EpCAM is a cell adhesion molecule. Its structure, its expression and the oncogenic potential, and its signaling network and target therapy were in concise reviewed. In recent advances, in addition to PI3K/akt and Raf/MAPK pathway involving in cell survival, anti-apoptosis and proliferation, and malignant initiation and progression, three distinct pathway are illustrated: EpCAM/E-cadherin-catenin-actin cytoskeleton, EpCAM/wnt/catenin signaling and its major EpCAM/nuclear signaling presented by Maetzel D in 2009 and Munz M in 2004. Moreover, more accumulated data are needed in detail mechanism. The data may provide its cancer biology and clinical targeting therapy benefits.

Keywords: EpCAM, nuclear signaling, structure, target therapy.

INTRODUCTION
In a series of long list of oncogenic receptors which discriminated tumorigenic in partial origin of tumors from receptors in normal health people and then better to potential targeting therapy benefits are presented in clear in previous references (Table 1)1.6. Because It is no need to targeting receptors in normal condition, actually, targeting therapy now is shift mainly toward oncogenic receptors in tumours in tumor hospitals, even if we won't citing in literature 7. EpCAM molecule a novel oncogenic receptor is shift toward new member family and targeting its antibodies34. In this article recent advances on EpCAM in this field are deliberated. The epithelial cell adhesion molecule [EpCAM] was originally identified as a tumor associated antigen in discovery in 1970s36, also known as cluster of differentiation 326 (CD326, and tumor-associated calcium signal transducer 1 (TACSTD1)37. EpCAM is a type I transmembrane protein of 314 amino acids (aa) with apparent molecular weight of 40KD. The extracellular domain (EpEX) contain epidermal growth factor-like domain, a thyroglobin (TY) repeat domain, transmembrane domain (TM) and a short 26-amino acid intracellular domain (EpICD (Figure 1))34-37. EpCAM is an oncogenic receptor that requires regulated intramembrane proteolysis for activation of its signal transduction capacity34. EpCAM cleavage is dependent on cell-to-cell contact. Thus, EpCAM as an oncogenic signaling protein engaged in cell adhesion and nuclear signaling35-38.

EpCAM expression, a dual player
EpCAM is expressed by the epithelium of health individuals (all simple, pseudo-stratified and transitional epithelia), except by squamous epithelium, and some specific epithelial cell types, such as hepatocytes and keratinocytes39. EpCAM is a membrane protein with proto-oncogenic properties that is expressed in most human carcinomas, EpCAM is over expressed to varying degrees39. These include the majority of adenocarcinomas including pancreatic adenocarcinoma, cholangiocarcinoma, node-positive breast cancer, epithelial ovarian cancer, lung cancer, colon carcinoma, prostate cancer, gastric cancer, hepatic carcinoma and squamous cell head and neck cancer41-43. Recently, EpCAM has been identified as an additional marker for cancer-initiating stem cells44-46. The oncogenic potential of EpCAM or EpICD was demonstrated in a mouse xenograft model, in which HEK 293 cells stably expressing EpCAM or EpICD produced nearly equivalent large tumours, whereas control cells only formed a small tumour in a single case. EpCAM expressing pancreatic cancer stem cells showed a 100-fold enhanced tumorigenic potential.
compared with EpCAM-negative pancreatic cancer stem cells.\textsuperscript{47,48} Similarly, in vivo evaluation of tumorigenicity in hepatocellular carcinoma cell lines, using immune deficient NOG mice, a smaller number of EpCAM\textsuperscript{+} cells (minimum 100) than EpCAM\textsuperscript{-} cells are able to tumor formation. The introduction of exogenous EpCAM into EpCAM\textsuperscript{+} clones, but not into EpCAM\textsuperscript{-} clones, markedly enhanced their tumor-forming ability.\textsuperscript{45} Also, EpCAM-positive hepatocellular carcinoma stem cells could efficiently initiate tumors in SCID mice.\textsuperscript{46} Very recent, EpCAM\textsuperscript{-} proliferating ductal cells (PDC) give rise to hepatocellular carcinoma (HCC) in the inflamed liver,\textsuperscript{48} which provide direct experimental evidence that EpCAM expressing PDC could be a cellular origin of HCC, suggesting the existence of stem/progenitor-derived hepatocarcinogenesis. For breast cancer stem cells, the ability to form tumors in SCID mice was for EpCAM\textsuperscript{+} cells 50-fold greater compared with the unfractioned tumor cells.\textsuperscript{47} Therefore, although EpCAM- and EpCAM\textsuperscript{+} cancer stem cells were able to form tumors, 10-fold less EpCAM\textsuperscript{+} cells than EpCAM- cells were able to induce tumors. Indeed, EpCAM over expression is associated with decreased overall survival of patients with a broad variety of carcinoma.\textsuperscript{42,47}

In contrast to its promoting role regarding tumor formation, high EpCAM expression only in two tumour types (renal clear cell carcinoma and thyroid carcinoma) has been consistently associated with improved patient survival.\textsuperscript{42,47}

### Table 1: Receptors with oncogenic potential associated with tumours (also receptor-mediated tumorigenesis)

| Growth factors receptors: | Oncogenic receptor EGFRvIII (GB, MLC, SCC\textsuperscript{8-11}), Oncogenic receptor MUC1\textsuperscript{12} or MUC4\textsuperscript{13}, Neu oncogenic receptor (breast cancer)\textsuperscript{14}, Oncogenic receptor IGF-1R\textsuperscript{14,28-29}
| Cytokine receptors | Oncogenic B receptor (HCD, CLL)\textsuperscript{16} and other VEGFR2 (colorectal cancer, glioma)
| Steroid receptors | Oncogenic growth hormone receptor (gigantism, acromegaly)\textsuperscript{15}, GHRH/GHRHR oncogenic signaling (pituitary tumors); Oncogenic EPO (PFCP)\textsuperscript{16}, oncogenic EPO-IGH/IGK fusion (BCP-ALL)\textsuperscript{17}, Oncogenic CSF3R (CNL or aCML)\textsuperscript{18}, IL-2-BCM fusion (T cell lymphoma); IL-3-IgH oncogenic fusion (ALL); IL-11/IL-11 receptor (gp130 Y757F/Y757F) pro-oncogenic signaling (gastric tumor in mice)\textsuperscript{19,20}, IL-21R-BCL6 fusion (DLBCL, lymphoma cell line; Oncogenic TSHR (thyroid adenoma)
| Others | Oncogenic thyroid hormone receptor (TR) (PTC)\textsuperscript{31}, Oncogenic THR1/BTR fusion (breast cancer cell line; oncogenic receptor pml/RARa (APL))\textsuperscript{22,23}, Oncogenic receptor AR variants (Pca)\textsuperscript{24-25}, ER pro-neoplastic signaling\textsuperscript{26-27}, neoplastic ESR1-CCDC170 fusion (also oncogenic receptor ERalpha fusion) (breast cancer)\textsuperscript{7,28}, GR\textsuperscript{beta} aberrant signaling (Cushing’s disease, erythrocytosis, GR\textsuperscript{beta} breast cancer, Nelson’s syndrome)\textsuperscript{29-31}, FSH/FSH receptor oncogenic signaling (preneoplastic ovarian surface epithelial cells)
| Tobacco related cancer (toxicology) | Pro-oncogenic receptor CLC1\textsuperscript{32}, nicotinic acetylcholine receptor alpha7-nAChR oncogenic receptor\textsuperscript{33}

![Figure 1: EpCAM structure](image-url)
Signal transduction by EpCAM oncogenic receptor and its target pathway
Several biological function of EpCAM has been described. EpCAM is a cell adhesion molecule, its action was invented in fact, is not limited on adhesion between cell and cell and also can activate intracellular MAPK and PI3K/Akt signal to cause tumor cell proliferation invasion and metastasis etc. biological action (Figure 2, George Zhu, 1991; Hu et al., 1)
Recent advances further uncovers a highlight of new data in its distinct signal pathway.

![Figure 2: A Scheme of oncogenic receptor (or receptor) mediated multiple signal transduction.](image)
(Here, nuclear regulators include transcriptional factors such as Jun/AP-1: Fos, NF-KB,mmyc, p53 and RB so on)
[Data from George Zhu, 1991; Science, 2002 (unpublished data)]

EpCAM/E-cadherin-catenin-actin cytoskeleton (E-cadherin-mediated adhesion)
Adhesion molecules are known to play an important role in defining cell fate, differentiation and other biological characteristics. EpCAM is a Ca\(^{2+}\)-independent homotypic intercellular adhesion molecule, thereby preventing cell scattering and likely to play a role in inhibition of invasion. Many studies have demonstrated that cadherin colocalized with EpCAM at the basolateral membrane in epithelial cells decrease adhesions mediated by E-cadherin, a family of Ca\(^{2+}\)-dependent homophilic cell-to-cell adhesion molecule. In epithelia cadherins are crucial for the establishment and maintenance of epithelial cell polarity, morphogenesis of epithelial tissues and regulation of cell proliferation and apoptosis.

Furthermore the adhesion function of E-cadherin depends on their association with regulatory proteins such as alpha- and beta-catenin. Catenins link cadherins with the actin cytoskeleton and can also form complexes with other epidermal growth factor receptor (EGFR) protein. EpCAM is able to abrogate E-cadherin-mediated cell-cell adhesion by disrupting the link between alpha-catenin and F-actin thereby loosening cell-cell adhesion and to rearrange the cytoskeleton of the cell. This negative effect of EpCAM expression on cadherin-mediated adhesion may explain the association of EpCAM expression with invasion and metastasis in epithelial carcinoma. EpCAM SiRNA treatment increased the cytoskeleton-anchored fractions of E-cadherin alpha-catenin and beta-catenin, then markedly decreased cell migration.
and cell invasion in the breast cancer cell line MDAMB-231 \textit{in-vitro} \cite{41}, which implicated that EpCAM as a regulator of cell adhesion is a potential novel target for breast cancer therapy.

\textbf{EpCAM/wnt-beta-catenin signaling}

Wnt proteins are a family of highly conserved signaling molecules that regulate cell-to-cell interaction during embryogenesis \cite{41,54}. Wnt binds to receptors of the Fzll (Frizzled) family on the surface. Through several cytoplasmic relay components, the signal is transduced to beta-catenin, which accumulates initially in the cytoplasm, and then enters the nucleus where it binds a lymphoid enhancer factor/T-cell factor transcriptional factor. The beta-catenin and lymphoid enhancer factor/T-cell factor complex further activates the expression of many target genes such as c-myc, VEGF and others, known to be associated with tumor development \cite{54}. It has been demonstrated that EpCAM silencing in breast cancer cells decreases the availability of beta-catenin for the wnt pathway and then silencing the activation of its target genes \cite{44}. This notion is also supported by Yamashita in patients with hepatocellular carcinoma and Kimura \cite{45,46}, in hepatocellular carcinoma cell lines. Their experiments uncovered that EpCAM-associated tumorigenicity in PLC/PRF/5 cells might be mediated by EpCAM-independent signaling due to the immunostaining failed to detect Epcam and EpCAM molecules in the nuclei of any cells from the PLC/PRF/5 cell lines. Moreover, the hepatic stem cell marker EpCAM knockout in EpCAM- cells reduces their colony-forming ability suggesting an important role for EpCAM in the EpCAM- cells and regardless of the exogenous expression of EpCAM. EpCAM- clones still had higher expression of c-myc, than the EpCAM- over-expressing EpCAM- clones. Therefore signals through EpCAM induce Wnt/beta-catenin activation might be involved to another different signaling pathway in tumorigenesis under certain condition \cite{45-47}.

\textbf{EpCAM nuclear signaling}

A highlight of new data presented by M. Munz that unravelled the entire pathway of EpCAM signalling from the cell membrane into nucleus \cite{45}. EpCAM was identified as a signal transducer \cite{58}; regulated transmembrane proteolysis by tumor necrosis factor-alpha-converting enzyme (TACE) cleaves EpEX and EpICD is cleaved by presenilin-2. Upon cleavage the extracellular domain EpEX is release as a soluble ligand while the intracellular domain EpICD translocates into the cytoplasm and enter the nucleus. EpICD associates with the adaptor protein FHL2 (four and a half LIM domain protein 2, beta-catenin and the transcription factor Lef-1. This transcription complex binds the DNA at the lef-1 consensus sites inducing target genes c-myc and cyclin A and E expression \cite{48}, and drives cell proliferation. This notion is supported by the EpCAM found in nuclei of colon carcinoma but not of normal tissue \cite{48}, and HCT (colon) and MCF-7 (breast) carcinoma cells \cite{45}. In addition, analysis for concomitant presence of claudin 7, Co-029, CD44V6 and EpCAM expression in the presence of all four molecules in a complex formation was initially found in colorectal cancer (CRR) and has been shown to facilitate metastasis \cite{49}. Others, epithelial-specific Ets-1 and Sp1 play an active role in EpCAM promoter regulation \cite{50}, while transcription factor nuclear factor-kappa B (NF-κB) and p53 have been described as transcriptional repressor of EpCAM \cite{47}, TACE-dependent EGFR axis \cite{49}. Claudin-7 and claudin-1 trafficked into lysosomes \cite{48} and presenilins mediate PI3K/akt and ERK activation via select signaling receptors \cite{9}, which present a highlight mechanism in cancer. The emerging function of EpCAM in cell proliferation, migration and possibly cancer initiation broadens the interest to use EpCAM as an immune target, antibody-based clinical trials and in 2009, the European Medicines Agency approved the use of tri functional bi specific antibody Catumaxomab, which binds to EpCAM oncogenic receptor and enhances the immunological response against EpCAM-positive cells in malignant ascites \cite{49}. Effects of monoclonal antibody immunotherapy was initially trials on patients with gastrointestinal adenocarcinoma \cite{46}, three of 20 patients with metastasis of gastrointestinal malignancies have no detectable disease for 10,13 and 22 months due to the treatment with an anti-colorectal cancer mouse monoclonal antibody 1083-17-1A of the IgG2α immunotherapy. In 1989-91, Zhu is the first to conduct that targeting therapy is shift toward oncogenic receptor [also surface-to-nucleus molecular missile therapy at that period, Zhu, 1980s] \cite{46,49}. In 1994, mAb17-1A (later named edrecolomab) was also the first to show clinical efficacy in a human cancer indication in terms of prolonged overall survival \cite{49}. Now, several anti-EpCAM therapeutic antibodies have been developed (edrecolomab, ING-1, 3622W94, adecatumumab) \cite{49}. The most prominent example is adecatumumab (MT201, a fully human IgG1 antibody that target oncogenic EpCAM, which was well tolerated by patients with hormone-refractory prostate cancer and in patients with rising prostate specific antigen (PSA) levels after radical prostatectomy \cite{43}. It is at present reaching phase III trial \cite{49}. In preclinical study, moreover, high doses of chiHEA125-Ama (100µg/Kg with respect to alpha-amanitin) administered 1 week apart, lead to complete tumor regression in 9 of 10 (90%) mice, suggesting that anti-EpCAM antibody conjugates with alpha-amanitin have the potential to be highly effective therapeutic agents for pancreatic carcinoma and various EpCAM-expressing malignancies. Targeting EpCAM oncogenic receptor might be a promising approach to stop tumor initiation, invasion and progression.

\section*{ACKNOWLEDGEMENTS}

We wish to convey our special thanks to Prof. Yosef Yarden to review this manuscript in Weizmann Institute of Science, Israel. We wish to thank Prof. T. Taniguchi in University of Tokyo in Japan, Nobel Laureates Prof. Ferid Murad in University of Texas Health Center in USA and UNESCO Science Laureates Prof. Atta-Ur-Rahman in international center for

\vspace{4cm}}
chemical and biological sciences, University of Karachi in Pakistan for their valuable help.

REFERENCES

1. Zhu G. Oncogenic receptor hypothesis (1989-91). Voice of America (VOA) 1992:12:31 https://doi.org/10.19080/JETR.2019.04.555643
2. Green S, Champon P. Carcinogenesis: A superfamily of potentially oncogenic hormone receptors. Nature 1986; 324:615-617. https://doi.org/10.1038/29215A0
3. Zhu G, Musueneci F, Byrne P. Induction of thyroid neoplasm following plant medicine marine algae (sargassum: A rare case and literature. Curr Pharm Biotechnol 2013; 14:859-863. https://doi.org/10.2174/138920101566614011309946
4. Singh RR, Kumar R. Steroid hormone receptor signaling in tumorigenesis. J Cell Biochem. 2005; 96:490-505.
5. Robinson R. Tumor cells share oncogenic receptors. J Cell Biol 2008; 181:570. https://doi.org/10.1083/jcb.1814r3
6. Neil JC, Fulton R, McFarlane R, Rigby M, Stewart M, Terry A, et al. Receptor-mediated leukaemogenesis: hypothesis revisited. Br J Cancer Suppl 1988; 9:76-79. PMID: 2855466
7. Zhu G, Saboor-Yaraghi AA, Yarden Y, Santos J, Neil JC. Down regulating oncogenic receptor: From bench to clinic. Hematol Med Oncol 2016;(1):30-40 https://doi.org/10.1086/jc.h.1814r3
8. Al-Nedawi K, Meehan B, Micaleff J, et al. Intracellular transfer of the oncogenic receptor EGFRvIII by microvesicles derived from tumor cells. Nat Cell Biol. 2008; 10:619-24. https://doi.org/10.1038/ncll2725
9. Miltra S, Han S, Soderstrom K, Wong A. Preferential expression of an oncogenic receptor in brain tumor stem cells. Identification and targeting using an engineered antibody. Cancer Res 2012; 72. https://doi.org/10.1083/jcb.1814r3
10. Hembrough T, Thyparambil S, Liao WL, Darfler M, Kritzman D et al. Quantitative multiplexed SRM analysis of oncogenic receptors in FFPE colorectal carcinoma tissue. Cancer Res 2012;72(8):5537. https://doi.org/10.1158/1538-7445.AM2012-5537
11. Koduri K, Gallant JN, Chae YK, Giles PS, Gitlitz BJ et al. EGFR fusions as novel therapeutic targets in lung cancer. Cancer Discov 2016; 6:601-11. https://doi.org/10.1158/2159-8290.CD-16-0075
12. Gabitova L, Gorin A, Astsaturov I. Molecular pathways: steroids and receptor signaling on cancer. Clin Cancer Res 2014; 20:28-34. https://doi.org/10.1158/1078-0432.CCR-13-0122
13. Duarte HO, Bolnamia M, Mereiter S, Osorio H, Gomes J, Reis CA. Gastric cancer cell glycosylation as a modulator of the ErB2 oncogenic receptor. Int J Med Sci 2017; 18(11):2262. https://doi.org/10.3892/ijms.18122622
14. Staudt LM. Therapeutic strategies in lymphoma based on oncogenic B receptor and MYD signaling. International Symposium on childhood 2012; 1:1. https://doi.org/10.1615/CritRevOncog.2017020816
15. Conway-Campbell BL, Woolf JW, Brooks AJ, et al. Nuclear targeting of the growth hormone receptor results in dysregulation of cell proliferation and tumorigenesis. Proc Natl Acad Sci USA 2007; 104:13331-13336. https://doi.org/10.1073/pnas.0600181104
16. Longmore GD, Pharr P, Neumann D, et al. Both megakaryocytepoiesis and erythropoiesis are induced in mice infected with a retrovirus expressing an oncogenic erythropoietin receptor. Blood 1999; 82(8):2386-95.
17. Russell LJ, De Cadro DG, Griffiths M, et al. A novel translocation, t (14; 19) (q32; p13, involving IGH and the cytokine receptor for erythropoietin. Leukemia 2009; 23:614-617. https://doi.org/10.1038/leu.2008.250
18. Maxson JE, Golli J, Polley DA, et al. Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. N Engl J Med 2013; 368:1781-90. https://doi.org/10.1056/NEJMoa1214514
19. Merchant JL. What lurks beneath: IL-11, via stat-3, promotes inflammation-associated gastric tumorigenesis. J Clin Invest 2008;118(5):1628-31 https://doi.org/10.1172/JCI35344
20. Ernst M, Najdovska M, Grail D, et al. STAT3 and STAT1 mediate IL-11-dependent and inflammation-associated gastric tumorigenesis in gp130 receptor mutant mice. J Clin Invest 2008;118:1727-38. https://doi.org/10.1172/JCI34944
21. Park JW, Zhao L, Willingham M, Cheng SY. Oncogenic mutations of thyroid hormone receptor beta. Oncotarget 2015; 6(10):8115-31. https://doi.org/10.18632/oncotarget.3466
22. Zhu G, Mishe E, Seigener B. Novel treatment of acute promyelocytic leukemia: A2023303 retinoic acid and retinoid pharmacology. Curr Pharm Biotechnol 2013; 14:849-858. https://doi.org/10.2174/1389201015666140113095812
23. Hauksdottiri H, Privalsky ML. DNA recognition by the abberant retinoic acid receptor implicated in human acute promyelocytic leukemia. Cell Growth Differ 2001; 12:85-98. PMID: 11243468
24. Berger R, Febo PG, Majumder PK, Zhao JJ, Mekherry S, et al. Androgen-induced differentiation and tumorigenicity of human prostate epithelial cells. Cancer Res 2004; 64:8867-8875. https://doi.org/10.1158/0008-5472.CAN-04-2938
25. Paltoglous S, Das R, Townley SL, et al. Novel androgen receptor co-regulator GRHL2 exerts both oncogenic and antimetastatic functions in prostate cancer. Cancer Res 2017; 77(13):3417-30. https://doi.org/10.1158/0008-5472.CAN-16-1616
26. Ludwik KA, McDonald OG, Brenin DR, et al. ER alpha-mediated nuclear sequestration of RSK2 is required for ER+ breast cancer tumorigenesis. Cancer Res 2018 15,78(8); 2014-2025. https://doi.org/10.1158/0008-5472.CAN-17-2063
27. El-shenawy I, Dubrovskiy O, Kastrati I, et al. Coactivation of estrogen receptor and IKKbeta induces a dormant metastatic phenotype in ER+positive breast cancer. Cancer Res 2017, 78(4):1-11. https://doi.org/10.1158/0008-5472.CAN-17-1686
28. Veeraraghavan J, Tan Y, Cao XX, et al. Recurrent ESRCCDC170 rearrangement in an aggressive subset of oestrogen receptor-positive breast cancer. Nat Commun. 2014; 5:8577. https://doi.org/10.1038/ncancer.2014.863
29. Varricchio L. The dominant negative beta isoform of the glucocorticoid receptor is uniquely expressed in erythroid cells expanded from polycythemia vera patients. Blood 2011;118:425. https://doi.org/10.1182/blood-2010-07-296921
30. Melhem A, Yamada SD, Fleming GF, Delgado B, Bridle DR, et al. Administration of glucocorticoids to ovarian cancer patients is associated with expression of the anti-apoptotic genes SGK1 and MKP1/DUSP1 in ovarian tissues. Clin Cancer Res 2009; 15:3196-3204. https://doi.org/10.1158/1078-0432.CCR-08-2131
31. Ebisawa T, Tojo K, Tajima N, Kaino M, Oki Y, et al. Immuno histochemical analysis of 11-beta-hydroxysteroid dehydrogenase type 2 and glucocorticoid receptor in subclinical Cushing’s disease due to pituitary macroadenoma. Endocrine Pathol 2008; 19:252-260. https://doi.org/10.1007/s12022-008-9052-0
32. Murray E, Hernychova L, Scigelova M, et al. Quantitative proteomic profiling of pleomorphic human sarcoma identifies CLIC1 as a dominant pro-oncogenic receptor expressed in diverse sarcoma types. Oncotarget 2014; 13:2543-59. https://doi.org/10.1021 forced 401071S
33. Zhao Y. The oncogenic functions of nicotinic acetylcholine receptors. J Oncol 2016; (3):1-9 https://doi.org/10.1155/2016/9650481
34. Denzel S, Maetzel D, Mack B, et al. Initial activation of EpCAM cleavage via cell-to-cell contact. BMC Cancer 2009; 9:402. https://doi.org/10.1186/1471-2407-9-402

35. Litvinov SV, Bakker HA, Gourevitch, et al. Evidence for a role of the epithelial glycoprotein 40 (EpCAM) in epithelial-cell-cell adhesion. Cell Adhes Commun 1994; 2:417-28. https://doi.org/10.3109/15419069409004452

36. Herlyn D, Herly M, Ross AH, et al. Effective selection of human tumors growth-inhibiting monoclonal antibodies. J Immunol Methods 1984; 72:157-67. https://doi.org/10.1016/0022-1759(84)90041-3

37. Baeuerle PA, Gires O. EpCAM (CD326) finding its role in cancer. Br J Cancer 2007; 96 (3):417-23. https://doi.org/10.1038/sj.bjc.6602949

38. Maetzel D, Denzel S, Mack B, et al. Nuclear signalling by tumour-associated antigen EpCAM. Nat Cell Biol 2009; 11:162-71. https://doi.org/10.1038/ncl10824

39. Winter MJ, et al. Expression of EpCAM shifts the state of caderhin mediated adherins from strong to weak. Exp Cell Res 2003; 285:50-58. https://doi.org/10.1016/S0092-8674(03)00045-9

40. Went P, et al. Frequent high-level expression of the immunotherapeutic target Ep-CAM in colon, stomach, prostate and lung cancers. Br J Cancer 2006; 94:128-35. https://doi.org/10.1038/sj.bjc.6602924

41. Osta WA, Chen Y, Mikhitarian K, et al. EpCAM is over expressed in breast cancer and is a potential target for breast cancer gene therapy. Cancer Res 2004; 64:5818-24. https://doi.org/10.1158/0008-5472.CAN-04-0754

42. Spizzo G, Went P, Dinrhofer S, et al. High Ep-CAM expression is associated with poor prognosis in node negative breast cancer. Breast Cancer Res Treat 2004; 86:207-213. https://doi.org/10.1023/B:BREA.0000067878.59816.01

43. Moldenhauer G, Salnikov AV, Luttgau S, et al. Therapeutic potential of EDG1 and EpCAM-conjugated anti-epithelial cell adhesion molecule monoclonal antibody agonist pancreatic carcinoma. J Natl Cancer Inst 2012; 104:622-34. https://doi.org/10.1093/jnci/djr1140

44. Ng YV, Ang SN, Chan JX, Choo AB. Characterization of epithelial cell adhesion molecule as a surface marker on undifferentiated human embryonic stem cells. Stem Cells 2009. https://doi.org/10.1111/j.1541-0546.2009.01661.x

45. Kimura O, Takahashi T, Ishii N, et al. Characterization of the epithelial cell adhesion molecule (EpCAM) +cell population in hepatocellular carcinoma cells line. Cancer Sci 2010; 101, 2145–55. https://doi.org/10.1111/j.1349-7006.2010.01661.x

46. Yamashita T, Budhu A, Forgues M, et al. Activation of hepatic stem cell marker EpCAM by Wnt-beta-catenin signalling in hepatocellular carcinoma. Cancer Res 2007, 67:10831-10839. https://doi.org/10.1158/0008-5472.CAN-07-0908

47. Van der Gun BTF, Melchers LJ, Ruiters MHJ, De Leij LFMH, McLaughlin PMJ, et al. EpCAM in carcinogenesis: the good, the bad or the ugly. Carcinogenesis 2010; 31(11):1913-21. https://doi.org/10.1093/carcin/bgp187

48. Matsumoto T. Proliferating EpCAM-positive ductal cells in the inflamed liver give rise to hepatocellular carcinoma. Cancer Res 2017; 77(22); 6131–43. https://doi.org/10.1158/0008-5472.CAN-17-1800

49. Ensinger C, Kremser R, Frommberger R, et al. EpCAM over expression in thyroid carcinomas: a histological study of 121 cases. J Immunoth 2006; 29:569. https://doi.org/10.1186/jcp.2011.090078

50. Gumbiner BM. Cell adhesion: the molecular basis of tissue architecture and morphogenesis. Cell 1996; 84:345-57. https://doi.org/10.1016/0092-8674(95)81279-9

51. Basak S, et al. Colorectal carcinoma invasion inhibition by Co17-1AGA733 antigen and its murine homologue. J Natl Cancer Inst 1998; 90:691-97. https://doi.org/10.1093/jnci/90.9.691

52. Takeichi M, Hatta K, Nose A, et al. Cadherin-mediated specific cell adhesion and animal morphogenesis. Ciba Found Symp 1989; 144:243-9. https://doi.org/10.1002/9780470513798.ch14

53. Hosthetzky H, Aberle A, Kernier R. Beta-catenin mediates the interaction of the cadherin-catenin complex with epidermal growth factor receptor. J Cell Biol 1994; 123:1375-80. https://doi.org/10.1083/jcb.123.5.1375

54. Huelsenk J, Behrens J, The Wnt signalling pathway. J Cell Sci 2002; 115:3977-8.

55. Munz M, et al. The carcinoma-associated antigen EpCAM upregulates c-myc and induces cell proliferation. Oncogene. 2004; 23:5748-58.

56. Kuhn S, Koch M, Nibel T, Ladwein M, Antolovic D, Klingbeil P, et al. A complex of EpCAM, claudin-7, CD44 variant isoforms, and tetraspanin promotes colorectal cancer progression. Mol Cancer Res 2007; 5(6):553-567. https://doi.org/10.1158/1541-7786.MCR-06-0384

57. Kenny PA, Bissell MJ. Targeting TACE-dependent EGFR ligand shedding in breast cancer. J Clin Invest 2007; 117:337-345. https://doi.org/10.1172/JCI29518

58. Wu CJ, Mannan P, Lu M, et al. Epithelial cell adhesion molecule (EpCAM) regulates claudin dynamics and tight junction. J Biol Chem 2013; 288:12253-68. https://doi.org/10.1074/jbc.M113.457499

59. Kang DE, et al. Presenilins mediate phosphatidylinositol 3-kinase/AKT and ERK activation via select signalling receptors. Selectivity of PS2 in platelet-derived growth factor signalling. J Biol Chem 2005; 280:31537-54.

60. Sears HF, Herly D, Stepowksi Z, et al. Effects of monoclonal antibody immunotherapy on patients with gastrointestinal adenocarcinoma. J Biol Response Med 1984; 3:138-50. PMID: 6374043

61. Carpenter G, Red Bremer M. EpCAM: another surface-to-nucleus missile. Cancer Cell 2009; 15:165-66. https://doi.org/10.1016/j.ccell.2009.02.005

62. Riethmueller G, Holz E, Schlimok G, Schmiegel W, Raab R, et al. Monoclonal antibody therapy for resected Dukes’ colorectal cancer: seven-year outcome of a multicenter randomized trial. J Clin Oncol 1998; 16:1788-94. https://doi.org/10.1200/JCO.1998.16.5.1788

63. Adkins JC, Spencer CM. Edrecolomab (monoclonal antibody 17-1A. Drugs 1998; 56:619-26. https://doi.org/10.2165/00003495-19985604-00001

64. Kurtz JE, Dufour P. Adevatumumab anti-EpCAM monoclonal antibody, from the bench to the bedside. Expert Opin Biol Ther 2010; 10(6):951-8. https://doi.org/10.1517/14712598.2010.482098