Drugs of the Future 2007, 32(10): 925-930

CCC: 0377-8282/2007
DOI: 10.1358/dof.2007.032.10.1123776

N-cadherin: a novel target for cancer therapy?

Lloyd Kelland
Head of Biology, Cancer Research Technology Development Laboratories, Wolfson Institute for Biomedical Research, University College London, Gower Street, London WC1E 6BT, U.K. Correspondence: lkelland@cancertechnology.com

CONTENTS

Abstract

The cadherins are a superfamily of transmembrane proteins integral to cell-cell adhesion. Increased N-cadherin, usually concomitant with loss of E-cadherin, often occurs during tumor progression as part of the epithelial-mesenchymal transition largely driven through the transcription factors Twist, Snail and SIP1. Hereby tumors acquire a highly motile and invasive phenotype. N-cadherin has been shown to be overexpressed in several common solid adult tumors, including prostate, colon, breast, pancreatic and bladder cancer. Ectopic expression of N-cadherin in breast cancer cells resulted in increased motility, invasion and metastasis, primarily via fibroblast growth factor (FGF) signaling and increased activity of the matrix metalloproteinase MMP-9. Knockdown of N-cadherin in cancer cells results in decreased migration, invasion and metastasis, as well as apoptosis via Akt/PKB pathway signaling. N-cadherin also plays a role in the maintenance of tumor vasculature and in tumor angiogenesis. The first N-cadherin antagonist to enter clinical trials for the treatment of cancer is ADH-1, a cyclic pentapeptide containing the N-cadherin histidine-alanine-valine (HAV) extracellular domain cell adhesion recognition motif. Preclinical studies with ADH-1 demonstrated apoptotic and tumor vessel angiolytic properties. In patients, ADH-1 appears to be well tolerated and can be safely administered at weekly i.v. doses of up to 500 mg/m^2. ADH-1 is currently undergoing phase II trials as monotherapy and various phase I combination trials with cytotoxics such as docetaxel, carboplatin, capecitabine or melphalan.

Introduction

Current cancer drug discovery and development is largely focused on harnessing the various biological properties that all malignant tumors possess. These "hallmarks" of cancer include uncontrolled growth (achieved through a combination of activation of oncogenes, unlimited replicative potential, inactivation of tumor suppressors and evasion of apoptosis), the formation of a blood supply (angiogenesis) and an ability to migrate and invade tissues, thereby metastazing to distant locations in the body (1). In the past decade, many of the underlying molecular players controlling these hallmarks have been identified, resulting in a plethora of new targets for cancer drug developers to attack.

However, before embarking on a cancer drug discovery program against a new target, there are two broad issues that need to be considered in detail. The first regards target validation. Questions include how prevalent the target is in human cancers and is the target activated, mutated or overexpressed and a driver of a particular cancer hallmark? To address possible links between the target and a cancer phenotype, use is often made in the laboratory of cancer cells in which levels of the target have been genetically manipulated; for example, knockdown by dominant negative mutants or by small interfering RNA (siRNA), or conversely, levels elevated by ectopic transfection. The second criterion is how "druggable" is the target? For example, is the target an enzyme or a protein-protein interaction, or present on the cell surface or within the nucleus. This review describes the evidence to support N-cadherin as a therapeutic cancer target and the current status of a molecule, the peptidyl N-cadherin antagonist ADH-1, which has entered early clinical trials in cancer patients.

N-cadherin: target validation

The cadherins are a superfamily of more than 80 transmembrane glycoproteins in humans that mediate calcium-dependent cell-cell adhesion through homophilic interactions (see Ref. 2 for review). Different members of the cadherin family are found in various cell types: type I

members E-cadherin in epithelial tissue, N-cadherin in neurons, P-cadherin in placenta, R-cadherin in the retina, and the type II cadherins (such as vascular endothelial VE-cadherin and cadherin-5 through -12). The cadherins are differentially expressed during normal embryonic development, where N-cadherin is a key molecule during gastrulation and neural crest development. The different cadherins share a high degree of sequence homology and consist of a large extracellular *N*-terminus domain, a single membrane-spanning region and a highly conserved cytoplasmic intracellular domain. Calcium binds to the extracellular domain, inducing a conformation that initiates and stabilizes the binding of cadherin subtypes on adjacent cells. Through the intracellular domain, the cadherins bind to catenins and other anchoring actin cytoskeletal and signaling molecules (see below).

In the context of cancer, much of the interest in the cadherins has arisen from the hijacking in many tumors of epithelial-mesenchymal transitions (EMT), a process vital for morphogenesis during embryonic development (2, 3). During gastrulation, cells undergo EMT, leading to the expression of N-cadherin and downregulation of E-cadherin in the mesoderm, a switch regulated by various transcription and growth factors. During EMT, cell-cell junctions are disrupted, there is extensive reorganization of the actin cytoskeleton and cells acquire increased migratory properties. Similarly, during EMT in carcinomas, which represent 90% of all malignant tumors, E-cadherin is often downregulated, while N-cadherin is upregulated (see Refs. 3 and 4 for reviews). The increase in N-cadherin is associated with increased invasiveness and metastatic behavior, but may not be essential for the morphological changes that accompany EMT (5).

In recent years, N-cadherin has been reported as a prognostic marker of cancer progression in several tumor types, including prostate, colon, breast, pancreatic and urothelial cancer (Table I). Early translational studies in prostate cancer had correlated the loss of E-cadherin expression with invasiveness and metastasis (6). Later, an immunofluorescence study was performed involving surgical specimens of prostatic adenocarcinoma, nonmalignant prostate tissue and pelvic lymph node metastases with detection of E-cadherin, N-cadherin and cadherin-11 (7). N-cadherin was expressed in high-grade cancers, whereas no expression was found in normal prostatic tissue. For 83 specimens of prostate cancer, 19% (4/21) of samples stained positive for N-cadherin where the Gleason score was 4-6 (indicative of relatively low-grade cancer), whereas 70% of samples were positive where the Gleason score was 8-10 (high-grade cancer), and 87% of lymph node metastases were positive. In most cases, the expression of N-cadherin and E-cadherin seemed to be mutually exclusive, *i.e.*, expression of N-cadherin was observed in samples that showed reduced or no staining for E-cadherin.

Similarly, in specimens of pancreatic cancer, N-cadherin expression was observed in 13/30 primary tumors and in 8/15 metastatic tumors (8). N-cadherin expression significantly correlated with neural intrapancreatic invasion, histological type, FGF2 expression in primary tumors, transforming growth factor (TGF) expression and the presence of vimentin. Another immunohistochemical study in 80 cases of colon carcinoma reported cytoplasmic and/or membrane-associated immunoreactivity of N-cadherin in 35 (44%) cases (9). Interestingly, N-cadherin was expressed almost exclusively in samples showing normal E-cadherin expression, highlighting a possible role for N-cadherin in primary colon cancer progression by exerting a dominant function over endogenous E-cadherin. Similar results have been seen in breast cancer cell line studies (see below). In breast cancer specimens (n=114), increased N-cadherin expression in comparison to E-cadherin was particularly associated with invasive micropapillary carcinoma of the breast (MPAP), which has a high propensity for lymphatic invasion and lymph node metastasis (10). N-cadherin staining was reported in 76% of MPAP cases and 52% of non-MPAP carcinomas. Finally, N-cadherin was proposed as a novel independent prognostic marker of tumor progression in a study of 101 superficial urothelial cancers (11). N-cadherin expression was absent from normal urothelium, but appeared in early-stage tumors and increased in later stage tumors. In most cases, expression was associated with loss of E-cadherin.

Studies using cancer cell lines have assisted in the elucidation of the phenotypic consequences of increased N-cadherin (and decreased E-cadherin). Expression of N-cadherin in a human squamous cell carcinoma-derived cell line was associated with a scattered fibroblastic phenotype (12). Moreover, transfection of this cell line with antisense N-cadherin resulted in reversion to a normal-appearing squamous epithelial cell with increased E- and P-cadherin expression, while transfection of N-cadherin into a normal-appearing squamous epithelial cell line resulted in downregulation of both E- and P-cadherin and a scattered fibroblastic phenotype (12). Second, forced expression of N-cadherin in noninvasive E-cadherin-positive breast cancer cells produced an invasive cell, even

Table I: N-cadherin expression in adult solid tumors.

Tumor type	Comment	Ref.
Prostate	No staining in normal prostate; increased staining in high-grade primary and metastatic nodules	7
Pancreatic	Expression correlated with intrapancreatic neural invasion	8
Colon	Positive staining in 44% of cases, usually with normal E-cadherin expression	9
Breast	Correlation with an aggressive invasive micropapillary carcinoma	10
Superficial urothelial	Independent prognostic marker for stage/tumor progression	11

though the cells continued to express high levels of E-cadherin (13). Also, transfection of a weakly metastatic and E-cadherin-positive breast cancer cell line (MCF7) with N-cadherin resulted in increased migration, increased invasion of Matrigel and more efficient adherence to monolayers of human umbilical vein endothelial cells (HUVEC) (14). When injected into the mammary fat pad of nude mice, the N-cadherin-transfected cells (but not the parent cell line) metastasized widely to the liver, pancreas, salivary gland, omentum, lung, lymph nodes and lumbar spinal muscle. Furthermore, only the N-cadherin-positive cells responded to the growth factor FGF2 by dramatically upregulating levels of MMP-9. Further studies by this group identified a signaling pathway leading to metastasis controlled by N-cadherin and the FGF receptor (15). Hereby, in the presence of N-cadherin, FGF2 caused a sustained activation of the MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) signaling pathway, leading to MMP-9 gene transcription and increased invasion. This occurred through N-cadherin protecting the FGFR1 from FGF ligand-induced internalization/downregulation.

A recent study from this group used transgenic mice co-expressing N-cadherin and polyomavirus middle T antigen in the mammary epithelium (16). These mice displayed increased lung metastasis but no change in tumor time of onset or growth, with tumors containing higher levels of phosphoERK and p38MAPK. Isolated tumor cells exhibited increased ERK activation, motility, invasion and MMP-9 expression in comparison to middle T antigen controls. N-cadherin has also been shown to promote survival and migration of melanoma cell lines (17) and to be involved in the adherence of malignant T-cells to epithelia (18). In the melanoma cell line study, blockade of N-cadherin-mediated intercellular interactions by N-cadherin-specific antibodies increased the number of cells undergoing apoptosis through a mechanism involving Akt/PKB-mediated inactivation of the proapoptotic protein BAD. N-cadherin also promoted migration of melanoma cells over a monolayer of dermal fibroblasts.

Other studies using cell lines also demonstrate that increased N-cadherin may contribute to cell survival and drug resistance. For example, in prostate cancer cell lines, signal transduction from N-cadherin resulted in anti-apoptotic signaling via the phosphatidylinositol 3-kinase (PI3K)-dependent activation of Akt/PKB and upregulation of the antiapoptotic protein Bcl-2 (19). Furthermore, a study using lymphoblastic leukemia cells from Bcr-Abl/P190 transgenic mice and grown with fibroblast stromal support showed that increased resistance to a clinically used farnesyltransferase inhibitor, SCH-66336, occurred when cells were forced to overexpress N-cadherin by lentiviral infection (20).

There is also emerging information concerning some of the molecular players that may lie upstream of N-cadherin and lead to its increased expression (Fig. 1). Key players in EMT and the loss of E-cadherin are transcription factors including the zinc finger proteins Snail (and the closely related Slug) and SIP1, and particularly the basic helix-loop-helix protein Twist (21, 22). Ectopic

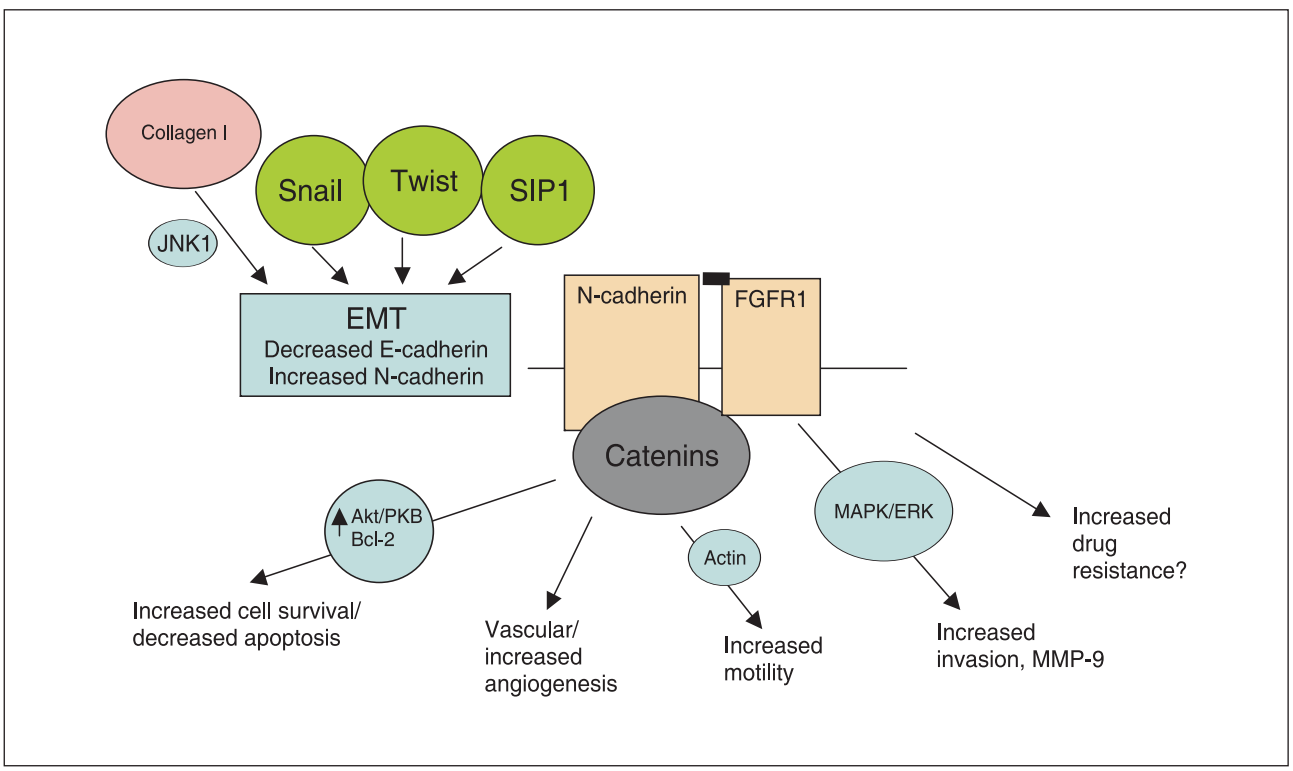


Fig. 1. Major roles of N-cadherin pathways in the cancer phenotype.

expression of Twist results in loss of E-cadherin-mediated cell-cell adhesion, activation of mesenchymal markers and the induction of cell motility (21). Conversely, suppression of Twist in highly metastatic breast cancer cells specifically inhibited their ability to metastasize to the lung (21). Furthermore, the gain in N-cadherin expression in prostate cancer has been shown in PC-3 cells to be associated with β_1-integrin-mediated cell adhesion to fibronectin and concomitant nuclear accumulation of Twist (23). Similarly, upregulation of gastric cancer cell invasion by Twist has been reported to be associated with expression of N-cadherin and fibronectin (24).

In other studies, the promotion of metastasis of BxPC-3 pancreatic cancer cells has been shown to involve collagen I signaling to activate c-Jun *N*-terminal kinase 1 (JNK1) and upregulate N-cadherin expression (25). Also in this study, knockdown of N-cadherin using short-hairpin RNA (shRNA) completely inhibited collagen I-induced cell scattering. Furthermore, cells knocked down for N-cadherin and injected orthotopically into the pancreas of mice formed significantly smaller tumors than did mock-infected cells, while cells overexpressing N-cadherin showed many disseminated tumor nodules. Finally, the tumor suppressor TIP30, the expression of which is altered in liver, prostate, lung, colon and breast cancers, has recently been shown to be linked to N-cadherin expression (26). Human hepatocellular carcinoma cells (HepG2) harboring an inactivating mutation of TIP30 showed upregulation of N-cadherin and decreased E-cadherin. Knockdown of N-cadherin using siRNA in these cells resulted in a marked reduction in cell viability and increased sensitivity to cisplatin-induced apoptosis.

In addition to the above-described role of N-cadherin in EMT and tumor progression, there is also evidence to support a role for N-cadherin in tumor vascular maintenance and tumor angiogenesis (see Refs. 27 and 28 for reviews). Whereas VE-cadherin is endothelium-specific and the major constituent of adherens junctions, N-cadherin is abundantly expressed in the endothelium. Specific deletion of N-cadherin from endothelial cells in mice resulted in embryonic lethality due to severe vascular defects (29). These studies suggest that N-cadherin may play a role in modulating VE-cadherin expression and is important for endothelial cell proliferation and motility.

Together, these studies suggest that elevated N-cadherin is associated with the progression of several major solid tumor types in the clinic and increased invasion, metastasis and tumor cell survival, as well as tumor angiogenesis (Fig. 1). Moreover, several studies using downregulation of N-cadherin in cancer cells support targeting N-cadherin using antagonists as a novel cancer therapy.

Targeting N-cadherin in cancer patients

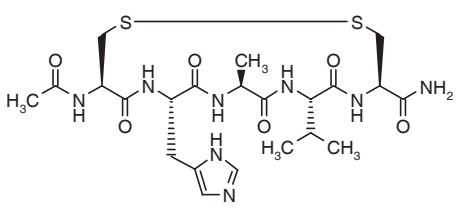
ADH-1: an N-cadherin antagonist

In terms of targeting N-cadherin, the classical cadherins are composed of 5 extracellular domains, the first of which (ECD1) contains an evolutionarily conserved histidine-alanine-valine (HAV) motif which was identified as being critical for function and is a cell adhesion recognition sequence (30). Linear peptides harboring this motif (*e.g., N*-Ac-LRAHAVDING-NH_2) were shown to be capable of inhibiting cadherin-dependent effects such as neurite outgrowth (31). Additional studies showed that when the HAV motif is flanked by an aspartic acid and thereby mimics the natural HAVD sequence of N-cadherin, this peptide becomes a much more selective inhibitor of N-cadherin function (32). A short cyclic peptide comprising *N*-Ac-CHAVC-NH_2 was shown to inhibit the N-cadherin component of neurite outgrowth over a 3T3 mouse fibroblast feeder layer and thereby act as an effective N-cadherin antagonist (32). The concentration required for 50% inhibition was around 300 μM.

The CHAVC (cysteine-histidine-alanine-valine-cysteine) containing cyclic peptide was further evaluated *in vitro* in cultured endothelial cells, either murine capillary cells (H5V) or bovine capillary endothelial cells (BCAP). Addition of the peptide to confluent cells for 24 h at a final concentration of 250 μg/ml and above resulted in apoptosis (33). This apoptosis was blocked by the addition of bFGF and also did not occur with cells actively proliferating at low density (subconfluent). Furthermore, tyrosine phosphorylation of FRS2, a specific FGFR1 substrate, was blocked by the peptide. Hence, the peptide appears to exert its effect via inhibition of N-cadherin-mediated activation of FGFR signaling.

The cyclic pentapeptide described above *N*-Ac-CHAVC-NH_2), manufactured and developed by Adherex Technologies and named ADH-1 (**1**), is currently in phase II clinical trials. Additional preclinical studies using ADH-1 confirm the *in vitro* findings described above, where a concentration of 500 μM caused cell death in HUVECs, while a concentration of 1 mM was required to cause death of PC-3 prostate cancer cells or TSU-Pr1 N-cadherin-positive bladder cancer cells (34). At the doses used, ADH-1 was inactive in an *ex vivo* rat aortic ring assay (at concentrations up to 200 μM) and against subcutaneously implanted N-cadherin-positive PC-3 prostate tumor xenografts at a dose of 200 mg/kg/day i.p. 5 days a week for 4 weeks (34).

Clinical and some additional preclinical findings with ADH-1 have been published in abstract form arising from various cancer conferences over the past few



ADH-1 (**1**)

years, and updates in the form of press releases have been reported by Adherex (www.adherex.com). In general, ADH-1 exerts its anticancer effects by two distinct mechanisms of action: apoptosis and tumor vessel angiolysis (see Ref. 35 for review). In a recent report, synergistic antitumor activity was observed in mice bearing A2780 ovarian carcinoma xenografts when ADH-1 (100 mg/kg i.p. b.i.d. for 21 days) was combined with the taxane paclitaxel (36). ADH-1 monotherapy using the same dosing schedule was ineffective. In a study of N-cadherin-overexpressing human pancreatic BxPC-3 cancer cells, ADH-1 (at a concentration of 200 μg/ml) prevented collagen I-induced cell scattering and migration and induced apoptosis. When these cells were implanted orthotopically into the pancreas of mice, ADH-1 (50 mg/kg/day 5 days a week for 4 consecutive weeks) slowed down tumor growth and decreased metastatic spread (37).

In two phase I monotherapy trials involving 70 patients, ADH-1 was well tolerated and demonstrated evidence of antitumor activity in 7 of 49 patients whose tumors expressed N-cadherin. ADH-1 was well tolerated when given at i.v. doses of 500-600 mg/m^2 either weekly or every 3 weeks in a phase IIa safety and efficacy trial in 40 patients with various N-cadherin-expressing solid tumors (38). No complete or partial responses were observed, although stable disease for up to 12 cycles of treatment was seen in a few patients. Commonly reported adverse events were pain (75%), fatigue (63%), vomiting (50%) and constipation (50%). ADH-1 pharmacokinetic analyses showed a biphasic profile with an initial half-life of about 12 min and a mean terminal-phase half-life of around 2 h. Currently, ADH-1 is being studied in combination with docetaxel, carboplatin or capecitabine or, in patients with melanoma, melphalan.

The future possibility of small-molecule, nonpeptide antagonists of N-cadherin has been highlighted by the preliminary identification of potent inhibitors at Adherex (www.adherex.com).

Conclusions

In recent years, N-cadherin has emerged as an attractive novel cancer target. This is based on both expression analyses from a variety of common solid tumors (*e.g.,* prostate, colon, breast) and evaluation of the biological consequences of knocking down or overexpressing N-cadherin in cancer cell lines. Increased N-cadherin represents a key aspect of EMT of carcinomas, resulting in increased invasion and metastasis. A role in maintaining tumor vascular endothelium and angiogenesis has also been demonstrated. A cyclic peptide-based inhibitor mimicking the HAV extracellular domain adhesion recognition sequence of N-cadherin is currently undergoing clinical studies as both monotherapy and in combination with conventional cytotoxic chemotherapy. While these studies are currently still at an early stage, ADH-1 appears to be well tolerated and safe as weekly doses of up to 500 mg/m^2.

References

1. Hanahan, D., Weinberg, R.A. *The hallmarks of cancer*. Cell 2000, 100(1): 57-70.

2. Derycke, L.D.M., Bracke, M.E. *N-cadherin in the spotlight of cell-cell adhesion, differentiation, embryogenesis, invasion and signalling.* Int J Dev Biol 2004, 48(5-6): 463-76.

3. Thiery, J.P. *Epithelial-mesenchymal transitions in tumour progression.* Nat Rev Cancer 2002, 2(6): 442-54.

4. Hazan, R.B., Qiao, R., Keren, R., Badano, I., Suyama, K. *Cadherin switching in tumor progression*. Ann NY Acad Sci 2004, 1014: 155-63.

5. Maeda, M., Johnson, K.R., Wheelock, M.J. C*adherin switching: Essential for behavioural but not morphological changes during an epithelium to mesenchyme transition*. J Cell Sci 2005, 118(Pt. 5): 873-87.

6. Umbas, R., Isaacs, W.B., Bringuier, P.P. et al. *Decreased E-cadherin expression is associated with poor prognosis in patients with prostate cancer.* Cancer Res 1994, 54(14): 3929-33.

7. Tomita, K., van Bokhoven, A., van Leenders, G.J.L.H. et al. *Cadherin switching in human prostate cancer progression.* Cancer Res 2000, 60(13): 3650-4.

8. Nakajima, S., Doi, R., Toyoda, E. et al. *N-cadherin expression and epithelial-mesenchymal transition in pancreatic carcinoma.* Clin Cancer Res 2004, 10 (12, Pt. 1): 4125-33.

9. Rosivatz, E., Becker, I., Bamba, M. et al. *Neoexpression of N-cadherin in E-cadherin positive colon cancers.* Int J Cancer 2004, 111(5): 711-9.

10. Nagi, C., Guttman, M., Jaffer, S. et al. *N-cadherin expression in breast cancer: Correlation with an aggressive histologic variant-invasive micropapillary carcinoma*. Breast Cancer Res Treat 2005, 94(3): 225-35.

11. Lascombe, I., Clairotte, A., Fauconnet, S. et al. *N-cadherin as a novel prognostic marker of progression in superficial urothelial tumors.* Clin Cancer Res 2006, 12(9): 2780-7.

12. Islam, S., Carey, T.E., Wolf, G.T., Wheelock, M.J., Johnson, K.R. *Expression of N-cadherin by human squamous carcinoma cells induces a scattered fibroblastic phenotype with disrupted cell-cell adhesion.* J Cell Biol 1996, 135(6, Pt. 1): 1643-54.

13. Nieman, M.T., Prudoff, R.S., Johnson, K.R., Wheelock, M.J. *N-cadherin promotes motility in human breast cancer cells regardless of their E-cadherin expression.* J Cell Biol 1999, 147(3): 631-44.

14. Hazan, R.B., Phillips, G.R., Qiao, R.F., Norton, L., Aaronson, S.A. *Exogenous expression of N-cadherin in breast cancer cells induces cell migration, invasion and metastasis.* J Cell Biol 2000, 148(4): 779-90.

15. Suyama, K., Shapiro, I., Guttman, M., Hazan, R.B. *A signalling pathway leading to metastasis is controlled by N-cadherin and the FGF receptor.* Cancer Cell 2002, 2(4): 301-14.

16. Hulit, J., Suyama, K., Chung, S. et al. *N-cadherin signaling potentiates mammary tumor metastasis via enhanced extracellular signal-regulated kinase activation.* Cancer Res 2007, 67(7): 3106-16.

17. Li, G., Satamoorthy, K., Herlyn, M. *N-cadherin-mediated intercellular interactions promote survival and migration of melanoma cells*. Cancer Res 2001, 61(9): 3819-25.

18. Makagiansar, I.T., Yusuf-Makagiansar, H., Ikesue, A., Calcagno, A.M., Murray, J.S., Siahaan, T.J. *N-cadherin involvement in the heterotypic adherence of malignant T-cells to epithelia.* Mol Cell Biochem 2002, 233(1-2): 1-8.

19. Tran, N.L., Adams, D.G., Vaillancourt, R.R., Heimark, R.L. *Signal transduction from N-cadherin increases Bcl-2.* J Biol Chem 2002, 277(36): 32905-14.

20. Zhang, B., Groffen, J., Heisterkamp, N. *Increased resistance to a farnesyltransferase inhibitor by N-cadherin expression in Bcr/Abl-P190 lymphoblastic leukemia cells.* Leukemia 2007, 21(6): 1189-97.

21. Yang, J., Mani, S.A., Donaher, J.L. et al. *Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis.* Cell 2004, 117(7): 927-39.

22. Yang, J., Mani, S.A., Weinberg, R.A. *Exploring a new twist on tumor metastasis.* Cancer Res 2006, 66(9): 4549-52.

23. Alexander, N.R., Tran, N.L., Rekapally, H., Summers, C.E., Glackin, C., Heimark, R.L. *N-cadherin gene expression in prostate carcinoma is modulated by integrin-dependent nuclear translocation of Twist1.* Cancer Res 2006, 66(7): 3365-9.

24. Yang, Z., Zhang, X., Gang, H. et al. *Up-regulation of gastric cell invasion by Twist is accompanied by N-cadherin and fibronectin expression.* Biochem Biophys Res Commun 2007, 358(3): 925-30.

25. Shintani, Y., Hollingsworth, M.A., Wheelock, M.J., Johnson, K.R. *Collagen 1 promotes metastasis in pancreatic cancer by activating c-Jun NH2-terminal kinase 1 and up-regulating N-cadherin expression.* Cancer Res 2006, 66(24): 11745-53.

26. Jiang, C., Pecha, J., Hoshino, I., Ankrapp, D., Xiao, H. *TIP30 mutant derived from hepatocellular carcinoma specimens promotes growth of HepG2 cells through up-regulation of N-cadherin.* Cancer Res 2007, 67(8): 3574-82.

27. Blaschuk, O.W., Rowlands, T.M. *Cadherins as modulators of angiogenesis and the structural integrity of blood vessels.* Cancer Metast Rev 2000, 19: 1-5.

28. Cavallaro, U., Liebner, S., Dejana, E. *Endothelial cadherins and tumor angiogenesis.* Exp Cell Res 2006, 312(5): 659-67.

29. Luo, Y., Radice, G.L. *N-cadherin acts upstream of VE-cadherin in controlling vascular morphogenesis.* J Cell Biol 2005, 169(1): 29-34.

30. Blaschuk, O.W., Sullivan, R., David, S., Pouliot, Y. *Identification of a cadherin cell adhesion recognition sequence.* Dev Biol 1990, 139(1): 227-9.

31. Doherty, P., Rowlett, L.H., Moore, S.E., Mann, D.A., Walsh, F.S. *Neurite outgrowth in response to transfected N-CAM and N-cadherin reveals fundamental differences in neuronal responsiveness to CAMs.* Neuron 1991, 6(2): 247-58.

32. Williams, E., Williams, G., Gour, B.J., Blaschuk, O.W., Doherty, P. *A novel family of cyclic peptide antagonists suggests that N-cadherin specificity is determined by amino acids that flank the HAV motif.* J Biol Chem 2000, 275(6): 4007-12.

33. Erez, N., Zamir, E., Gour, B.J., Blaschuk, O.W., Geiger, B. *Induction of apoptosis in cultured endothelial cells by a cadherin antagonist peptide: Involvement of fibroblast growth factor receptor mediated signalling.* Exp Cell Res 2004, 294(2): 366-78.

34. Li, H., Price, D.K., Figg, W.D. *ADH-1, an N-cadherin inhibitor, evaluated in preclinical models of angiogenesis and androgen-independent prostate cancer.* Anti-cancer Drugs 2007, 18(5): 563-8.

35. Kelland, L. *ADH-1: An N-cadherin antagonist targeting cancer vascularisation.* Curr Opin Mol Ther 2007, 9(1): 86-91.

36. Gupta, M., Barnes, D., Losos, J., Spehar, G., Bednarcik, M., Peters, W.P. *Synergistic anti-tumor activity of ADH-1 in vitro and in vivo in combination with paclitaxel in ovarian cancer cell lines.* Proc Amer Assoc Cancer Res (AACR) 2007, 48: Abst LB-356.

37. Shintani, Y., Johnson, K.R., Wheelock, M.J. *ADH-1 suppresses N-cadherin-dependent pancreatic cancer progression.* Proc Amer Assoc Cancer Res (AACR) 2007, 48: Abst LB-261.

38. Chu, Q., Jonker, D.J., Knox, J. et al. *An open label safety and efficacy phase 2a study of the N-cadherin (N-cad) antagonist ADH-1 in subjects with N-cadherin expressing solid tumors.* J Clin Oncol [43rd Annu Meet Am Soc Clin Oncol (ASCO) (June 1-5, Chicago) 2007] 2007, 25(18, Suppl.): Abst 3567.