Adhesion Therapy: An Endogenous Bioactive Process

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ABSTRACT
Adhesions are fibrous bands that form between tissues and organs and natural part of the body’s healing process after surgery in the same way that a scar forms. Adhesion molecules are conventionally divided into four main groups as follows: selectins, the immunoglobulin gene superfamily, the integrins and the cadherins. There are two main families of cell adhesion molecules (CAMs); Calcium independent (Immunoglobulin (Ig) Superfamily, selectins, lymphocyte homing receptors) and Calcium dependent (Cadherins and Integrins). Adhesion molecules have important role in disease prognosis; some can be used as biomarkers for disease prognosis.

Key Words: Adhesion therapy, fibrous bands, adhesion molecules

INTRODUCTION
Adhesions are fibrous bands that form between tissues and organs, often as a result of injury during surgery. They may be thought of as internal scar tissue that connects tissues not normally connected. Adhesions form as a natural part of the body’s healing process after surgery in the same way that a scar forms. A study in digestive Surgery showed that more than 90% of patients develop adhesions following open abdominal surgery and 55%–100% of women develop adhesions following pelvic surgery. Regions affected are adhesive capsulitis and abdominal adhesions [1]. Adhesion to neighboring cells or to the extracellular matrix regulates multiple cellular processes such as cell migration, morphogenesis, proliferation, gene expression and cell survival [2]. Types of adhesion include fibrinous and fibrous adhesions. Adhesion process requires adhesion molecules which are glycoprotein molecules expressed on the surfaces of cells that assist cells in interacting with their environments through adherence. Adhesion molecules are conventionally divided into

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four main groups as follows: Selectins, Immunoglobulin gene superfamily, Integrins and Cadherins. Adhesion molecules play important role in normal and disease processes. Role of some adhesion molecules in disease as possible biomarkers has been enthusiastically investigated \[3\]. This review represents the study of adhesion therapy and adhesion molecules to promote development or invention of an ideal therapeutic agent that targets adhesion molecules for treatment of certain diseases.

**ADHESION THERAPY**

Cell adhesion occurs when a plasma membrane adhesion receptor interacts with a molecule in the extracellular matrix or on the neighboring cell and when the liganded receptor forms a connection with the cell’s own cytoskeleton. The reversibility of the process, which may oscillate through cycles of adhesion and detachment, enables cells to move with respect to one another or on the extracellular matrix. The process is controlled by the expression and function of adhesion receptors and by encounter with the corresponding ligands. Thus cell adhesion is a major theme in normal biological processes and pathological disturbances involving cell-cell and cell-matrix interactions. Examples include fertilization, embryogenesis, morphogenesis, tissue structure and repair, hemostasis and immune and inflammatory responses. Cell adhesion enables cells to be targeted to a particular location within tissues or in the body. In addition, many signaling molecules are docked in adhesion sites and their activation results in the production of messages which cross-talk with cell signaling pathways. Studies have shown that adhesion participates in the regulation of differentiation, proliferation and apoptosis. Thus cell adhesion has a dual morphogenetic and signaling function which explains its pleiotropic impact in normal biology and pathology \[4\].

![Cell adhesion](image)

**Figure 1: Cell adhesion**
Table 1: Adhesion receptor classification

<table>
<thead>
<tr>
<th>Adhesion receptor</th>
<th>Structural feature</th>
<th>Counter-receptor</th>
<th>Cellular function</th>
<th>Biological and pathological implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICAM, vCAM, MadCAM</td>
<td>IgG repeats</td>
<td>leucocyte-leucocyte-leucocyte-endothelium interactions</td>
<td>Leucocyte trafficking, Inflammatory and Immune responses</td>
<td></td>
</tr>
<tr>
<td>NCAM, L1, Thy1</td>
<td>IgG and fibronectin repeats</td>
<td>homotypic binding</td>
<td>neural cell-cell adhesion</td>
<td>Neural development and plasticity</td>
</tr>
<tr>
<td>Cadherins, Desmogleins, Desmocollins</td>
<td>cadherin repeats</td>
<td>homotypic Ca++ dependent binding</td>
<td>adherens junctions, - and desmosome components</td>
<td>Tissue structure and repair Invasion-metastasis</td>
</tr>
<tr>
<td>Selectins</td>
<td>sugar binding domain</td>
<td>sialomucins PSLG-1, ESL-1</td>
<td>leucocyte-endothelium interactions</td>
<td>Leucocyte rolling</td>
</tr>
<tr>
<td>Integrins</td>
<td>α/β heterodimers</td>
<td>Mg++- dependent binding of ligands on cell (CAM) and in ECM</td>
<td>promiscuous</td>
<td>promiscuous, all situations listed above</td>
</tr>
<tr>
<td>CD44</td>
<td>numerous splice variants</td>
<td>hyaluronans</td>
<td>cell-ECM interaction</td>
<td>Leucocyte activation and trafficking Invasion metastasis</td>
</tr>
</tbody>
</table>

**Modes of Cell Adhesion**

The interaction between cell adhesion molecules can be considered to be identical to the binding of a ligand to its receptor. This is an important concept because often the binding of two cells sets up intracellular signal transduction in the adherent cells. Basically, there are three ways cell adhesion molecules interact with each other.

Homophilic interactions involve two identical cell adhesion molecules while heterophilic interactions involve two different molecules.\(^5\)

**Families of Cell Adhesion Molecules**

There are basically two families of Cell Adhesion Molecules (CAMs): Calcium independent and Calcium dependent. Calcium independent consists of
Immunoglobulin (Ig) Superfamily, Selectins and Lymphocyte homing receptors. Calcium dependent family consists of Cadherins and Integrins [6]. The following graphic shows that Ig Superfamily (e.g., N-CAM) members and Cadherins are involved in homophilic interactions, while heterophilic interactions characterize the integrins and selectins.

Figure 2: Homophilic and heterophilic interactions of cell adhesion molecules

**Immunoglobulin Superfamily: N-CAM**

The first Cell Adhesion Molecules were called CAMs but CAMs comprise only the Ig Superfamily. N-CAM (Neural-Cell Adhesion Molecule) is one of dozens of CAMs but it was the first one that was characterized. It is a glycoprotein with 30% sialic acid residues by weight. It is a member of Ig Superfamily which mediates Ca\(^{2+}\)-independent cell adhesion [8].
Different Forms of N-CAM

N-CAM has been found in many different forms. Differing amounts of glycosylation, especially regarding amounts of sialic acid can alter the adhesivity of the molecule. In addition, alternative splicing of the primary RNA transcript leads to the production of different forms that have different functions in cells. The following diagram shows four forms of N-CAM.

Figure 3: N-CAM

Figure 4: Four forms of N-CAM
One form has a glycosylphosphatidylinositol (glycolipid) anchor. Another form is soluble. Thus this soluble N-CAM form could mediate a diversity of events as for the ectodomains of cadherins. Neural cell adhesion molecule is homophilic binding glycoprotein expressed on the surface of neurons, glia, skeletal muscle, neuroendocrine cells and natural killer cells. It has been implicated as having role in cell adhesion, neurite outgrowth, synaptic plasticity, learning and memory. Neural cell adhesion molecule is expressed in most neuroendocrine tumor types and antibodies to the common extracellular domain are therefore used in the diagnosis of these malignancies like lung carcinoma.

**Cadherins**

Cadherins are Ca\(^{2+}\)-dependent cell adhesion molecules which mediate binding to cytoskeleton and form part of cell junctions (desmosomes). E-Cadherin (Uvomorulin) is present in early embryonic development; replaced by N-Cadherin at gastrulation\(^{[2,5]}\).

There is a prominent linkage of cadherins with cancer. A diversity of factors transform normal epithelial cells into cancer cells which typically express reduced epithelial cadherin (E-Cad = E-cadherin). This loss of E-cadherin is directly linked to malignancy.
The soluble ectodomain (extracellular domain: sE-Cad or sE-cadherin) of cadherin is shed from the cell surface of developing cancer cells as a result of proteolytic cleavage. This cleavage is primarily directed by various MMPs (matrix metalloproteinases) and ADAM10 (a disintegrin and metalloproteinase) as well as some other proteases. A similar sequence of events converts N-Cad to sN-Cad. E-Cadherin is expressed in epithelial tissue where it is constantly regenerated with a five hour half life on the cell surface in desmosomes. Loss of E-cadherin function or expression has been implicated in cancer progression and metastasis. E-cadherin down regulation decreases the strength of cellular adhesion within a tissue resulting in an increased cellular motility used for diagnosis of different kinds of cancer. K-Cadherin is expressed in renal tubules and the alterations in it are associated with progression of renal cell carcinoma. The extracellular domain of OB-Cadherin is used to inhibit adhesion between prostate cancer cells and osteoblasts. Ep-CAM is used as a target for immunotherapy of human carcinoma.

**Integrins**

Integrins are heterodimers which mediate Ca²⁺-dependent adhesion and are the main way by which cells adhere to ECM. There are over twenty types of these molecules.⁵
Integrins are associated with various diseases like humans leukocyte adhesion deficiency, genetic defects, inability to make β2 Subunit, inability of WBCs to stick to endothelium; an initial step in fighting infections and inflammation and persistent bacterial infections.

**Table 2: Types of integrins**[7]

<table>
<thead>
<tr>
<th>INTEGRINS</th>
<th>LIGANDS</th>
<th>DISTRIBUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>α5β1</td>
<td>Fibronectin</td>
<td>Ubiquitous.</td>
</tr>
<tr>
<td>α6β1</td>
<td>Laminin</td>
<td>Ubiquitous.</td>
</tr>
<tr>
<td>α7β1</td>
<td>Laminin</td>
<td>Muscle.</td>
</tr>
<tr>
<td>α1β2</td>
<td>IgSF counter receptor</td>
<td>White blood cells.</td>
</tr>
<tr>
<td>α2β3</td>
<td>Fibrinogen</td>
<td>Platelets.</td>
</tr>
<tr>
<td>α6β4</td>
<td>laminin</td>
<td>Epithelial hemidesmosome</td>
</tr>
</tbody>
</table>

**Selectins**[5]

**Figure 7: Integrin**

**Figure 8: Selectins**
Selectins are found in glycolipids and glycoproteins and they bind to sialic acid glycoconjugates. They mediate Ca\(^{2+}\)-dependent Cell-ECM binding in blood. They are very important in binding of WBCs to endothelium as a part of inflammatory response. There are three types of selectin: E-selectin (in endothelial cells), L-selectin (in leucocytes) and P-selectin (in platelets and endothelial cells) \(^\[2\]\). Selectin plays an important role in inflammatory injury in different organs. It plays role in severe traumatic brain injury, multiple sclerosis tissue injury in stroke (increase selectin levels in CSF), thrombus formation enhanced, myocardial infarction (leukocyte adhesion increased in presence of platelets by involving platelet P-selectin). Selectin blockers i.e. selectin ligands inhibit leukocyte platelet interaction after arterial injury due to angioplasty; provide cardioprotection in case of coronary artery occlusion. In renal ischemia-reperfusion injury up regulation of P & E-selectins is present. Selectin blockade may be potential therapeutic intervention in, renal dysfunction & tissue damage. Antibodies directed against both L-&E-selectin reduce pulmonary leakage & neutrophil accumulation. In case of liver ischemia antibodies directed against both L-and E-selectin significantly reduce pulmonary leakage and neutrophil accumulation \(^\[8\]\). The list of important functions of adhesion molecules is long, but some of them are tissue, organ development and cell proliferation, reproductive physiology, embryogenesis, immune and inflammatory cell migration, starting and expanding immune response, interacting between cell and extracellular matrix, wound healing and cancer metastasis \(^\[9\]\).

Cell Adhesion process- Leukocyte migration to inflammed tissue

**Figure 9: Leukocyte migration to inflammed tissue**
Leukocyte adhesion molecules (LAMs) are expressed on leukocytes and other cell types and regulate many leukocyte functions. LAMs function in various biological processes such as development, signaling, inflammation and apoptosis. There currently exists a multistep paradigm of leukocyte emigration to inflamed tissue that involves specific leukocyte adhesion molecules. To emigrate into tissue, leukocytes initially tether to and roll on the vascular endothelium. This relatively loose adhesion is mediated by the selectin family of adhesion molecules and their ligands. Subsequent activation of leukocytes and the endothelium leads to firmer adhesion mediated through integrin adhesion molecules (e.g., CD18) and their receptors (e.g., intercellular adhesion molecule-1, ICAM-1). Leukocyte transmigration is the final stage and occurs between endothelial cells. Leukocytes then travel through the extracellular matrix to the source of tissue injury, guided by a concentration gradient of cytokines and chemokines produced at the site of injury. Adhesions form as a natural part of the body’s healing process after surgery in the same way that a scar forms. As a part of the process, the body deposits fibrin onto injured tissues. The fibrin acts like a glue to seal the injury and is the initial glue that builds the fledgling adhesion, said at this point to be "fibrinous". In body cavities such as the peritoneal, pericardial and synovial cavities, a family of fibrinolytic enzymes may act to limit the extent of the initial fibrinous adhesion, and may even dissolve it. In many cases however the production or activity of these enzymes is compromised because of injury and the fibrinous adhesion persists. If this is allowed to happen, tissue repair cells such as macrophages, fibroblasts and blood vessel cells, penetrate into the fibrinous adhesion, and lay down collagen and other matrix substances to form a permanent fibrous adhesion. While some adhesions do not cause problems, others can prevent tissues and organs from moving freely, sometimes causing organs to become twisted or pulled from their normal positions.

**Occurrence of Adhesion- Pathophysiology**

**Figure 10: Adhesion**

**Adhesion occurring Regions**

1. Adhesive capsulitis:
   In the case of frozen shoulder, also known as adhesive capsulitis, adhesions grow between the shoulder joint surfaces, restricting motion.
2. Abdominal adhesions:
   Abdominal adhesions, also known as intra-abdominal adhesions, are most commonly caused by abdominal surgical procedures but may also be caused by pelvic
inflammatory disease. The adhesions start to form within hours after surgery and may cause internal organs to attach to the surgical site or to other organs in the abdominal cavity. Adhesion-related twisting and pulling of internal organs can result in complications such as infertility and chronic pelvic pain. Surgery inside the uterine cavity can result in Asherman's Syndrome, also known as intrauterine adhesions, a cause of infertility.

3. Small bowel obstruction:
It is another significant consequence of post-surgical adhesions. A small bowel obstruction may be caused when an adhesion pulls or kinks the small intestine and prevents the flow of content through the digestive tract. It can occur 20 years or more after the initial surgical procedure, if a previously benign adhesion allows the small bowel to spontaneously twist around itself and obstruct. A small bowel obstruction is often an emergent condition that could result in death without immediate medical attention. According to statistics provided by the National Hospital Discharge Survey approximately 2000 people die every year in the USA from obstruction due to adhesions.[2] Depending on the severity of the obstruction, a partial obstruction may relieve itself with conservative medical intervention. However, many obstructive events will require re-operation to lyse the offending adhesions or resect the affected small intestine.

Types of adhesions

1. Fibrinous adhesions. These are causes of early postoperative obstruction which settles down within 3–5 days. The majority of fibrinous adhesions will disappear in due course of time.
2. Fibrous adhesions. If the infection is continuous or if foreign is present, the fibrinous material is converted into fibrous material.

Anti-adhesion therapy
The main goal of this therapy is to prevent adhesion between host tissues and pathogens to prevent the disease. For anti-adhesion therapy to be effective, it is probably necessary to use multiple agents.

Anti-adhesion therapy for bacterial diseases[10]
1) Receptor analogs:
There is evidence that receptor analogs as agents for anti-adhesion therapy would be practical primarily against pathogens that bind to animal cells via carbohydrate-specific adhesins (lectins). In these cases, the receptor analogs are saccharides that are structurally similar to those of the glycoprotein and glycolipid receptors for the adhesion and, therefore, act by competitive inhibition.
2) Adhesin analogs:
These analogs are based on assumption that isolated adhesin molecule or active synthetic or recombinant fragment binds to receptor and competitively block adhesion of bacteria.
3) Adhesin based vaccines:
Prevention of symptomatic infections by blocking adhesion using adhesin-based
Vaccines can be achieved either by active or passive means. Although active anti-adhesin immunity is expected to prevent infection by stimulation of secretory IgA on mucosal surfaces, significant amounts of serum IgG also appear to reach these surfaces, such as the gut, oral cavity and even the urinary tract. In passive immunity, the target host is treated with anti-adhesin antibodies made in another host. The best example of this is where the K88 fimbriae and related adhesins of farm animal pathogens were used to vaccinate the mothers so that the suckling piglets acquired milk-secreted antibodies which functioned to prevent infection by the pathogen. It has been assumed that these antibodies prevented infection by inhibiting adhesion.

4) Dietary inhibitor:
Some of the most efficient anti-adhesion agents identified thus far are present in foodstuffs. Foodstuffs containing either a mixture of inhibitors or an inhibitor with a broad spectrum of activity could be especially effective. Most effective anti-adhesive agents are present in diet i.e. in human milk or in some plants.

5) Sublethal concentrations of antibiotics:
Subinhibitory concentrations of antibiotics have been shown to reduce the ability of pathogens to adhere to various substrates.

6) Host derived anti-adhesins in innate immunity:
In recent years, increased attention has been given to immediate defense mechanisms based on non-clonal recognition of microbial components (i.e. innate immunity). One facet of this is the inhibition of adhesion of pathogens, and subsequent reduction of colonization by constituents in various body fluids is now known to be an important component of the innate immune system. Potential inhibitors of adhesion are abundant in body fluids, but only a few of them are there as evidence to suggest that they act to provide effective defense against pathogens.

**Drawbacks Anti-adhesion therapy**
1. Anti-adhesive agents are not bactericidal.
2. Major drawback of anti-adhesion therapy is that most pathogens possess genes encoding for more than one type of adhesin.

**Role of adhesion molecules**

1. Ischemic stroke \[11,12\]
Stroke is defined as rapidly developing clinical signs of focal or global disturbance of cerebral function with symptoms lasting 24 hours or longer, or leading to death with no apparent cause other than of vascular origin. The mortality rate after an ischemic incident is very high (30%) and survivors almost always face disabilities that require costly long term care. Ischemic stroke frequently results from thromboemboli blocking the blood supply to neuronal tissue. Since leukocyte-endothelial cell adhesion is a rate-determining step in the recruitment of leukocytes into post-ischemic brain tissue, much attention has been devoted to defining the contribution of different adhesion molecules, expressed either on leukocytes or endothelial cells, to the leukocyte recruitment process a large effort has been made to determine whether interference with
leukocyte-endothelial cell adhesion protects the brain against ischemic tissue injury. In inflammatory environment, cerebral endothelial cells increase their expression of cell surface adhesion molecules that mediate recruitment of leukocytes and platelets to the ischemic region.

Leukocyte adhesion in post-ischemic cerebral microvessels:
The recruitment of leukocytes and platelets in the cerebral microvasculature is widely regarded as a rate limiting step in the inflammatory response associated with cerebral ischemia. In response to an ischemic (or other inflammatory) insult, cerebral endothelium is capable of expressing high levels of adhesion molecules and recruiting large numbers of leukocytes.

Therapeutic targeting of leukocyte-endothelial cell adhesion

1. Selectin blockade

Following cerebral ischemia, P- and E-selectins are highly expressed at brain. P-selectin can be detected as early as 15 minutes after reperfusion while E-selectin expression is observed beginning 2 hours after ischemia. The expression of selectins contributes to the early recruitment of circulating cells to the infarct region56. The link between P-selectin expression and injury following ischemic stroke seems to involve a complement-dependent pathway wherein P-selectin up-regulation results from complement activation and can be modulated with a targeted approach to complement receptor 2 without an effect on systemic complement activity. The polysaccharide fucoidin, a homopolymer of sulfated L-fucose that competitively inhibits P- and L-selectin, has been shown to attenuate the leukocyte accumulation during reperfusion of the rat brain following focal ischemia. Fucoidin also reduced infarct size and improved neurological outcome, suggesting a role for selectin-dependent leukocyte-endothelial cell interactions following cerebral ischemia. However, L-selectin blockade with a humanized anti-L-selectin antibody did not decrease the tissue damage or number or infiltrating leukocytes to the ischemic region in a rabbit model of transient cerebral ischemia. Blocking E-selectin with specific antibodies as long as 90 minutes after onset of ischemia has been shown to reduce infarct size.

2. Intercellular adhesion molecule-1 blockade

Intercellular adhesion molecule-1 knockout mice exhibit a reduction in leukocyte adhesion, smaller infarcts, decreased leukocyte adhesion, improved cerebral blood flow and lower mortality after cerebral ischemia and reperfusion. Similarly, intercellular adhesion molecule-1 immunoblockade reduces ischemic brain injury and neutrophil accumulation in both rat and rabbit models of cerebral ischemia.

3. Lymphocyte function-associated antigen-1/ macrophage-1 antigen blockade

The expression of CD11a and CD18 is up-regulated in stroke patients and patients with transient ischemic attacks for up to 72 hours
after the ischemic incident, revealing an association between cerebral ischemia and the cell surface density of these adhesion molecules. Immunoblockade of either CD11b, CD18 or macrophage-1 antigen also affords protection against tissue injury. Similarly, CD18 immunoneutralization in rats reduces the edema, leukocyte infiltration and infarct size resulting from transient ischemia.

II. Atherosclerosis

Various inflammatory processes induce their expressions, such as atherosclerosis and cerebral ischemia, with the upregulations mediated by cytokines. Normally, vascular endothelial cells have low adhesiveness for leukocytes; however, when stimulated they express adhesion molecules at their surfaces responsible for adhesion and activation of leukocytes as a precondition for transendothelial migration of leukocytes.

III. Cancer

Adhesion molecules play an important role in normal and disease processes and are implicated in cancer invasion and metastasis. Cellular adhesion molecules of cadherin, integrin, and immunoglobulin superfamilies are important to both growth and metastasis of many cancers including malignant melanoma. Loss of intercellular adhesion and the desquamation of cells from the underlying lamina propria allows malignant cells to escape from their site of origin, degrade the extracellular matrix, acquire a more motile and invasion phenotype, and finally, invade and metastasize. In addition to participating in tumor invasiveness and metastasis, adhesion molecules regulate or significantly contribute to a variety of functions including signal transduction, cell growth, differentiation, site-specific gene expression, morphogenesis, immunologic function, cell motility, wound healing, and inflammation.

1. C-CAM1 or CEACAM1

In a 13-yr old juvenile prostate, C-CAM1 can be clearly found in the basal cell layer of all glands examined. And, the basal cell in the prostate has been suggested to represent a stem cell population. Therefore, C-CAM1 may play an important role in controlling prostate development. Loss of C-CAM1 expression is an early event in the development of prostate cancer. Similarly, several decreased C-CAM1 expression is found in several other tumor types. C-CAM1 is a potent tumor suppressor in prostate carcinogenesis.

2. DCC

Deletion in colon carcinoma (DCC) shares a similar Ig-like structure with C-CAM. It is a potential tumor suppressor gene. DCC is often found to be missing in various cancers, including prostate, bladder, gastric and colon. Expression of DCC can induce apoptosis in a variety of cancer cell lines.

3. Cadherin

Cadherin genes are considered as tumor suppressor genes and defects in their expression or function have been associated with tumor progression. The expression of cadherin in tumor cells can serve to trace the histologic origin of tumors and can be used
as differential diagnostic markers between tumors of similar phenotype but different histogenesis. The classical cadherins include E-, N-, and P-cadherin. E-cadherin mediates cell contact and acts as an important suppressor of epithelial tumor cell invasiveness and metastasis. N-cadherin is expressed in neuroectodermal and mesodermal-derived tissues. P-cadherin is found in mouse placenta, lung epithelial, basal cells of the skin, and myoepithelial cells of the mammary gland. The expression of P-cadherin in epithelial tissues is characteristic of cell populations with proliferative potential, and its expression decreases as cells differentiate. Cadherins associate with a group of intracellular proteins termed catenins, which link the cadherin molecules to the actin microfilaments and mediate signal transduction mechanisms that regulate cell growth and differentiation. Three catenins have been identified: α-, β-, γ-catenins. β- and γ-catenins form mutually exclusive complexes with α-catenins and bind to the carboxy-terminal cytoplasmic domain of cadherin molecules.

4. Integrins
Integrins are transmembrane glycoproteins consisting of α and β subunits. β integrins play an important role in metastatic cell migration in sarcoma Rous, bladder cancer, and colorectal cancer. β integrins also participate in signal transduction, as well as in oncogenesis, and cell growth processes. RGD (arginine-glycine-aspartic acid) sequence may be useful in the prevention of lung cancer metastases to other organs, since when they were intravenously administered to mice, no lung cancer metastases in other organs were observed. It is notable, that this RGD sequence represents the integrins epitope, carcinogenic transformation is clearly associated with alterations in the integrins expression. Integrins play an important role in cancer prognosis. They can be used as biomarkers for disease progression.

5. CD44
CD44 expression is associated with tumor development in colorectal cancer, breast cancer, bladder cancer, prostate cancer as well as in melanomas. CD44 is significantly decreased in metastatic cancer compared to matched primary cancer.

IV. Inflammatory bowel disease[16]
One of the more recent clinical advances in inflammatory bowel disease (IBD) therapy has been due to the recognition of the role of adhesion molecules in inflammation. These molecules regulate the “sticking” of inflammatory cells to a number of tissues and produce disease. The first clinical use of a specific antiadhesion therapy used antisense technology. First, the antisense acts at a transcriptional level, and therefore acts to prevent adhesion molecule expression. The antisense molecules have a molecular size that is much smaller than antibodies. This allows the antisense molecule to pass through the cell wall and act intracellularly. Antisense is a “mirror-image” of mRNA, and are oligonucleotides. These molecules bind to their specific, target
mRNA, and through RNase H-mediated hydrolysis cause degradation of their target mRNA. With chemical modifications of the antisense oligonucleotide, specific characteristics of its activity can be modified.

CONCLUSION
Adhesions are natural part of body’s healing process. Cell adhesion molecules play important role in this process and also in various diseases. While considering the future prospective role of adhesion molecules in treatment of various diseases, they should be studied in detail as they can be possible biomarkers in diagnosis and prognosis of various malignancies.

REFERENCES
