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Inhibition of Tumor Cell Growth with Therapies Using Small Molecules

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Key words: Inhibition tumor cell growth, small molecules, therapies

Over the recent years therapy in oncology has been dominated by advances in the field of pharmacogenomics. In its broadest definition, pharmacogenomics encompass studies of the genotype and phenotype of tumor cells that can predict the likelihood of response to a specific treatment. This treatment modality is called targeted therapy and includes not only chemotherapy treatments but also new type of treatments such as monoclonal antibodies and small molecules.

One of the first type of small molecule based treatment in oncology was the development of hormone therapies for patients with breast and prostate cancer. The drug tamoxifen is the most widely prescribed antiestrogen for the treatment of women with breast cancer expressing estrogen and progesterone receptors since 1970.During the last years additional biomarkers have been used to further refine hormone therapy responses that supported the introduction of new hormone treatments such as aromatase inhibitors

All-Trans Retinoic Acid (ATRA) has shown significant clinical benefit for patients with acute promyelocytic leukaemia that feature t(15:17) a disease defining translocation. Direct targeting of the retinoic acid receptor with ATRA results in high overall disease response rates, delay in disease progression, and long-term cures.

The introduction of Imatinib Mesylate (Gleevec) for patients with chronic myeloid leukaemia bearing the bcr/abl translocation was accompanied by a lot of excitement by the scientific and public communities for the future potential of low-toxicity, targeted anticancer therapy. Treatment with imatinib, an adenosine triphosphate–binding selective inhibitor of bcr-abl, has been associated with durable complete hematologic and complete cytogenetic remissions with minimal toxic effects in the early chronic phase of CML. Imatinib has also a role for the treatment of relapsed and metastatic gastrointestinal stromal tumors (GISTs), which characteristically bear an activating mutation in the c-kit receptor tyrosine kinase (RTK) gene.

Gefitinib was recently approved as monotherapy for patients with inoperable non–small cell lung cancer that fail to respond to chemotherapy treatment. Gefitinib is a small-molecule drug that targets epidermal growth factor receptor (EGFR) and is easily identified by immunohistochemical analysis. This receptor is found in lung and other cancers but multiple cellular biochemical pathways are involved in its regulatory function limiting the use of gefitinib to specific tumor phenotypes.

Erlotinib is a novel very promising inhibitor of EGFR in late-stage clinical trials for the treatment of non–small cell lung cancer, pancreatic cancer, and primary glioma.

Thalidomide, Endostatin, and Angiostatin) are small-molecule drugs that target tumor blood vessels (antiangiogenesis drugs) are in clinical trials for a variety of malignant neoplasms. Until today, the development of a test

(such as tumor microvessel density or the expression of an angiogenesis-promoting gene or protein) for the identification of patients that benefit more from this type of treatment has proved a difficult task. Nevertheless, its use in patients with refractory multiple myeloma has shown enormous clinical benefit.

Recently, drugs targeting the proteasome have been developed that are designed to impact downstream pathways regulating angiogenesis, tumor growth, cell adhesion, and resistance to apoptosis. One of these agents, bortezomib, was approved in May 2004 for the treatment of relapsed and refractory multiple myeloma. Bortezomib inhibits the nuclear factor kB (NFkB) and is under investigation for the treatment of early-stage multiple myeloma, non-Hodgkin lymphoma, and a variety of solid tumors, including lung cancer.

During the next several years, the field of oncology drug development will see numerous products pass through the approval process and enter the market accompanied by diagnostic tests designed to *personalize* their use, dosage, route of administration, and length of treatment for each patient, one at a time. Only time will tell whether this new approach to anticancer pharmaceuticals will yield breakthrough results, reducing morbidity and mortality and improving outcomes for all who will be afflicted with the disease.

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Inhibition of Cancer with Monoclonal Antibodies

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Key words: Monoclonal antibodies, cancer, inhibition

Monoclonal antibodies (MAbs) are capable of targeting certain antigens with remarkable specificity such as tumor associated antigens, growth factor receptors etc having the potential to destroy malignant cells by immunological mechanisms. MAbs have been used to treat a number of common malignancies either reacting with growth factor receptors (HER-2, $EGFR_{1, ...}$) or as active immunogens, activating cellular effector mechanisms (ADCC, complement activation, etc) or as carriers of toxins, drugs, enzymes, photosensitizers and radioisotopes. Preclinical as well as clinical studies with MAbs have led to some striking examples of antitumor effects. However, the majority of early trials served primarily to illustrate the obstacles to successful therapy, particularly when using unconjugated MAbs that are designed to stimulate and focus host immune responses on tumor sites. Current clinical data confirm that immunotherapy with MAbs is an effective treatment in a number of common malignancies including breast, colorectal and head and neck cancer, NHL and leukemias resulting in a significant reduction in mortality and tumor recurrence rates. Immunotherapy of certain tumors with MAbs has currently incorporated chemotherapy in order to improve clinical results either by eliminating residual drug-resistant tumor cells or sensitizing tumor cells to chemotherapy-induced apoptosis. Additional

studies are required in order to optimize the methods for enhanced antibody targeting in tumors, to reduce serious adverse events and identify subgroups in patients who might benefit more from immunotherapy with MAbs. The development of new molecules such as immune fragments, peptides, cancer specific and chimeric/humanized MAbs as well as anti-idiotypic antibodies is a major challenge currently in terms on how to integrate these new treatments to existing molecules. In conclusion, immunotherapy with MAbs represents an established new therapeutic anticancer modality. In the future, MAbs will have a far more increased impact on the management of patients with cancer.

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Safety and Immunogenicity of the Optimized Cryptic Peptide $TERT_{572Y}$ in Patients with Advanced Malignancies: A Phase I Clinical Study

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Key words: Optimized cryptic peptide $TERT_{572Y,}$ patients with advanced malignancies, phase I clinical study, safety, immunogenicity

Background: $TERT_{572Y}$, an optimized cryptic peptide homologous to TERT induces efficient antitumoral T cell cytotoxic immunity but not autoreactivity *in vivo* in HLA-A*0201 transgenic mice and healthy blood donors and prostate cancer patients (J. Clin. Invest., 2004, 113,425). A phase I trial evaluating the safety and immunogenicity of the cryptic $TERT_{572Y}$ peptide was conducted in HLA-A*0201 cancer patients.

Patients and methods: Nineteen patients with chemotherapy refractory and progressing malignant tumors were enrolled in the study. The vaccination protocol consisted of two injections of optimized $TERT_{572Y}$ peptide followed by four injections of native $TERT_{572}$ peptide. Peptides were injected emulsified in Montanide ISA51. Patients were vaccinated with escalated doses of peptide ranging from 2 to 6 mg. Toxicity and peptide-specific immune responses were evaluated.

Results: Fourteen patients completed the entire vaccination program. Only grade I toxicity was observed, affecting 13 of the 19 patients. $TERT_{572Y}$-specific cytotoxic T cells were detected in the peripheral blood of 13 out of 14 evaluate patients, as early as 3 weeks after the 2^{nd} vaccine injection. CTLs were fully functional and killed TERT-overexpressing tumor cells. Four (29%) of 14 evaluable patients experienced stable disease for a median of 10 months.

Conclusion: $TERT_{572Y}$ peptide vaccine is well tolerated and effective in eliciting a specific T cell immunity. This is the first clinical trial demonstrating that cryptic peptides are promising candidates for cancer immunotherapy.

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Human Autoimmune Disorders and Chronic Rejection of Organ Allografts are T-Cell Diseases Driven by Specific Antigens

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Key words: Human autoimmune disorders, organ allografts, T-cell diseases, specific antigens

We have shown that major autoimmune diseases and chronic rejection of organ allografts in humans are specific antigen-driven T-cell diseases. Our research group has used a combination of molecular and cellular approaches to reach these conclusions. These approaches include the examination of appropriate target tissues for: (i) the presence of infiltrating mononuclear cells (CD3-positive T cells) expressing early, intermediate and late activation antigens; (ii) the expression of T-cell derived cytokines (identified using DNA microarrays and other approaches); (iii) the presence of monoclonal/oligoclonal populations of alpha/beta T-cell receptor (TCR)-positive and gamma/delta TCR-positive T cells, identified by the presence of multiple identical copies of TCR transcripts in appropriate target tissues; and (iv) other evidence. Strong evidence suggest that: (i) osteoarthritis (OA) (in approximately 40-50% of the patients examined); (ii) systemic sclerosis (SSc); (iii) abdominal aortic aneurysms (AAA); (iv) demyelinating disease of the CNS; and (v) chronic rejection of cardiac allografts; are specific-antigen driven T-cell diseases and that T cells play a central role in their pathogenesis. Additionally, the immune response of the host to the tumor exhibits similar characteristics. Clonally expanded T cells in these diseases are of functional significance and very likely responsible at least in part for the initiation and/or the propagation of these autoimmune disorders, the rejection of organ grafts and the immune response of the host to the tumor. T cells provide the “engine” for the development and maintenance of chronic inflammation. Molecular mimicry is one of the possible mechanisms that may be involved. The identification of specific antigen-driven T-cell responses and of clonally expanded *in vivo* TCR transcripts in these diseases will permit the identification of specific antigens that elicit these responses and may be are responsible for the pathogenesis of these diseases. These results substantially improve our understanding of these disorders for which effective treatment is not available. A

number of these disorders need to be reclassified and new molecular and cellular approaches need to be developed incorporating our new understanding of these diseases to achieve more effective treatment protocols.

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Neurosteroids as Neuroprotectants

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Key words: Neurosteroids, neuroprotectants

The neuroactive steroids dehydroepiandrosterone (DHEA), its sulfate ester DHEAS and allopregnanolone (Allo), produced by the central nervous system and the adrenals, appear to exert a protective effect in hippocampal and cortical neuron ischemia- and excitotoxicity-induced injury (1,2). These steroids they may also play a protective role on the adrenal medulla, an important part of the sympathetic nervous system, and the tissue adjacent to their primary site of production. Indeed, DHEA, DHEAS and Allo protect rat chromaffin cells and the rat pheochromocytoma PC12 cell line, an established model for the study of adrenomedullary cell apoptosis and survival, against serum deprivation-induced apoptosis. Their effects are time- and dose-dependent with EC_{50} 1.8, 1.1 and 1.5 nM respectively (3). The anti-apoptotic effect of DHEA(S) and Allo is found to be structure-specific, confined mainly to conformation 3beta-OH-Δ^5 for androstenes and 3alpha-OH for pregnanes. Indeed, 3-keto, Δ^4, or C7 hydroxylated androstenes and 3beta pregnanes are ineffective. The prosurvival effect of DHEA(S) appears to be NMDA-, $GABA_A$-sigma1- or estrogen receptor independent, and is probably mediated by a specific G-protein coupled membrane receptor. It involves the anti-apoptotic Bcl-2 proteins, their role being sine-qua-non for their action since Bcl-2 antisense oligonucleotides reverse their effects. Furthermore, DHEA(S) and Allo activate CREB and NF-κB, up-stream effectors of the anti-apoptotic Bcl-2 proteins expression. They also activate most prominent pro-survival kinases, such as PKCα/β, MEK/ERK and PI3K/Akt. Our findings suggest that decline of DHEA(S) and Allo during ageing or stress may leave the adrenal medulla unprotected against proapoptotic challenges.

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Identification of Antigen(S) in Demyelinating Disease through Molecular Analysis of the T-Cell Receptor

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Key words: Demyelinating disease, antigen(S), T-cell receptor, molecular analysis

MS is an inflammatory demyelinating disease that may be initiated in genetically susceptible individuals by an as yet unidentified virus aquired at childhood. About 85% of the MS cases manifest as classical chronic remitting-relapsing and secondary progressive autoimmune demyelinating disease of the CNS. Clonally expanded T cells have been reported in the CNS of these patients with chronic MS, however, they may represent epitope spreading because of the chronic nature of these forms of MS. In contrast, short-term or acute MS are more appropriate to study in order to obtain information on T cells that may be involved in initiation or early propagation of the disease. To elucidate the role of T cells in the pathogenesis of the disease, we investigated the clonality of T cells present in the CSF or in brain plaques of patients with acute or short-term MS or MS-like disease. Multiple copies of identical α- and β-chain TCR transcripts were found demonstrating the presence of oligoclonal populations of T cells. To identify putative MS antigens recognized by T cells expanded in vivo, in brain plaques or the CSF of these patients we employed a molecular reconstitution strategy of the clonally expanded TCR. This approach involves the following steps: (1) construction of full-length copies of the clonally expanded α- and β-chain TCR transcripts; (2) expression of the full-length clonally expanded α- and β-chain TCR transcripts into αβ TCR-negative mutant Jurkat T cells using a retroviral vector; (3) determination whether these transduced Jurkat T cells with the clonally expanded TCR recognize, as determined by cytokine production, putative neuroantigen(s) or viral peptides presented by autologous antigen presenting cells (APC). Using the approach described above, we constructed and expressed in mutant Jurkat T cells full-length clonally expanded α- and β-chain TCR transcripts in the CSF of a patient with multiphasic disseminating encephalomyelitis (MS-like demyelinating disease) following infection with hepatitis A virus. These transduced T cells produce cytokines in response to a myelin peptide presented by autologous APC. This is a general approach that can be employed for the identification of putative antigens expressed on appropriate APC to engineered T cells expressing in vivo clonally expanded TCR.

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Cellular Activation and Cytokine Expression Profiles in Autoimmune Diseases and Organ Transplantation: Modulation by Therapeutic Peptides, Sparing the T Regulatory Cells

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Key words: Cellular activation, cytokine expression, autoimmune diseases, organ transplantation, therapeutic peptides, T regulatory cells

In autoimmune diseases, the immune system reacts against autologous antigens and causes cell and tissue damage. Autoimmune diseases are many, and they affect about 3% of the world population. The incidence of autoimmunity depends on genetics, sex and the environment. Today's central idea of autoimmunity involves an immune response of a genetically predisposed individual to an environmental pathogen under the influence of inadequate or non-functional immunoregulatory mechanisms (1-4). Advances in the treatment of autoimmune diseases, follow a better understanding of the abnormalities in the cellular activity pathways and the resulting, and often permanent, imbalance of the pro- and anti-inflammatory cytokine expression profiles (5,6). Over the past few years, there has been a dramatic change in the therapeutic regimens employed in autoimmune diseases, targeting defined pathways of the adaptive immune response. New therapeutic modalities, either in clinical practice or in the experimental stage, include monoclonal antibodies (mAbs), already in use in rheumatoid arthritis patients, vaccines, DNA vaccines and gene therapies. Another approach towards the therapeutic management of autoimmune diseases, involves the design and use of peptide analogs of disease-associated epitopes, to be used as immunomodulatory drugs (7,8). The mechanisms of peptide action that have been proposed so far include: (I) A peptide can act as an antagonist of the wild type antigen for TCR binding, thus interfering with the whole process of antigen presentation and T-cell activation; this can result to apoptosis or anergy of the auto-reactive T-cell clones. (II) A peptide can block or reduce T-cell proliferation and/or (III) induce the polarization of Th0 uncommitted cells to differentiate into anti-inflammatory Th2 cells (immune deviation). Finally, (IV) a peptide can induce peptide-specific regulatory T-cells that cross-react with cognate self-antigen (bystander suppression) (8-11). The peptides can thus arrest the ongoing inflammatory response, interrupt the adaptive memory response in both T- and B-cell compartments, and/or induce antigen-specific immunomodulation and establish tolerance (8-11). Our research group focuses on auto-antigen-specific peptides that meet certain constraints, i.e. they must suppress autoimmune activity

but, also, they must spare the regulatory T-cells (Tregs). Another approach to therapeutic peptides is the design and synthesis of peptide analogs that inhibit the binding of cytokines to their receptors. This approach is not antigen-specific, but aims to suppress the activation of T-cells by any antigen, at a very early stage. In this approach, the same peptides can be used for many disease states in which activated T-cells are major players in their pathology, such αs organtransplantation and certain types of autoimmune diseases. We are currently working towards the development of peptides that can block cytokine binding to their receptor and are suitable for *in vivo* use. As a working model, we use the interleukin 2 (IL-2)/IL-2 receptor (IL-2R) system: Human interleukin-2 (IL-2) is a major regulatory 15.5 kD cytokine (12,13). IL-2 is secreted primarily by activated naive helper T-cells (Th0) and, in turn, it activates helper T-cells (both Th1 and Th2 types), cytotoxic T-cells, B-cells, NK cells and macrophages (14,15). IL-2 binds to and mediates its biological effects through a receptor complex consisting of three distinct subunits (chains) designated IL-2Rβ (CD25), IL-2Rβ(CD122) and IL-2Rγ_c (CD132) (14). The IL-2Rβ and γ_c chains are also utilized by IL-15, a pleiotropic pro-inflammatory cytokine that is implicated in several inflammatory disorders (16). The exclusive expression of the high affinity IL-2R on the surface of activated T-cells makes it an attractive target for the selective inhibition of alloreactive T-cells in organ transplantation or self-reactive T-cells in type-1 autoimmune diseases. In the last 25 years, a lot of research has produced a plethora of anti-IL2R mAbs to be used in the treatment of a wide variety of heterogeneous diseases that have as common denominator high levels of IL-2R expression. The majority of anti-IL-2R mAbs that are used therapeutically in organ transplantation, recognize the α chain (17,18). Fairly recently, it was shown by many research groups that IL-2 promotes the thymic development and peripheral expansion of Tregs, an important population of T-cells that promotes immunological tolerance (19-21). Although Tregs in humans have diverse phenotypes, the majority are CD4CD25 T-cells. Thus, current treatments involving anti-IL-2Rα mAbs could diminish the Tregs/CD4CD25 populations also, leading, in the long term, to the development of severe type-1 autoimmune diseases. Therefore, developing therapeutic strategies that do not involve anti-IL-2Rα mAbs would lead to safer drugs for immunotherapy. To take this point further, replacing mAbs altogether by peptides that block cytokine binding to its receptor, thus inhibiting cell activation without destroying the receptor-bearing cells (through antibody-mediated complement lysis and/or opsonization), is an attractive prospect. Work in our group with peptides designed to map to epitopes of the IL-2Rβ, has produced encouraging preliminary results (22, 23): These particular amino acid sequences are putative IL-2 binding domains because they are located within epitopes recognized by monoclonal antibodies to the IL-2Rβ-subunit, that block binding of IL-2 to its receptor (22). Three of these peptides inhibited mitogen-induced proliferation of peripheral blood T-cells, and two of those had no effect on the percentage of the CD4CD25 T-cells (23). Future experiments will show whether these peptides have *in vivo* activity. In addition, we are currently working on synthetic peptide modifications in order to get molecules that will be stable enough for *in vivo* use.

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REVIEW OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS, INTERNATIONAL EDITION 20: 389-390 (2006)

Animal Models in Multiple Sclerosis: The Use of Myelin Altered Peptide Ligands

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Key words: Multiple sclerosis, myelin altered peptide ligands, animal models

Much of our knowledge regarding the underlying mechanisms in Multiple Sclerosis pathogenesis has been achieved through research on the principal animal model of the disease, the experimental allergic encephalomyelitis (EAE). Like MS, EAE is characterized by $CD4^+$-mediated inflammatory lesions in the central nervous system (CNS) followed by demyelination and axonal damage. Inflammatory infiltrates are consisted of T-cells that are activated against several myelin antigens that are vulnerable in autoimmune attack. Other inflammatory components like cytokines, chemokines, adhesion molecules, macrophages, complement activation and antibodies are also involved in the immune – mediated cascade of myelin destruction. In addition, the mechanism of action of a number of the currently used immunomodulating agents in MS therapy or those tested in ongoing clinical trials were first indicated in EAE. Among them are the altered peptide ligands (APL) which are native peptides modified by amino-acid substitutions at essential contact residues for the TCR. These agents can modulate T-cell responses to native peptide antigens implicated in the pathogenesis MS and EAE. However, their sensitivity to proteolytic enzymes as well as some immune - mediated side effects impose some difficulties in the use of these agents as MS therapeutics. A number of cyclic myelin peptide analogues seem to be potential candidates in maintaining the biological function of the original peptide and effective in EAE modulation. The potential mmunomodulating and neuroprotective properties of these agents, needs further investigation. Data from studies on EAE models, may introduce clinical trials designed to elucidate the impact of APL in

MS disease activity. These clinical trials should include clinical, neuroimaging and immunological outcomes.

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Monoclonal Antibody Natalizumab for the Treatment of Multiple Sclerosis

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Key words: Multiple sclerosis, treatment, monoclonal antibody, Natalizumab

Activated lymphocytes chemotactically move to the site of inflammation through the vascular system. The process of their extravasation is complicate and includes among others their adhesion to the blood vessel wall through adhesion molecules receptors, VCAM-1 and MadCAM-1. These molecules bind with transmembranic Alpha-4 integrins. Natalizumab is a monoclonal antibody against Alpha-4 integrins, arresting adhesion of lymphocytes on the endothelium, their extravasation and consequently the progress of the inflammatory process, characterizing Multiple Sclerosis.

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Immunomodulation in EAE through Regulation of T Helper Cell Subsets

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Key words: Experimental autoimmune encephalomyelitis, T helper cel subsets, regulation

The possibility to modulate the outcome of a disease by manipulations that induce the selective maturation of T helper cell subsets is a recurrent theme in biomedical research. It has been established, by using different experimental approaches, that favoring the maturation of type 2 helper cells inhibits the progression of CNS inflammation in experimental

autoimmune encephalomyelitis (EAE), the most widely used animal model of the disease multiple sclerosis (MS). Recent developments show that the protective effect might result from alterations on the different T cell pools of the organism such as effector, memory or regulatory T cells. An overview of the current approaches for the possible therapeutic utilization of such knowledge will be presented.

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The Contribution of Docking in the Rational Drug-Design

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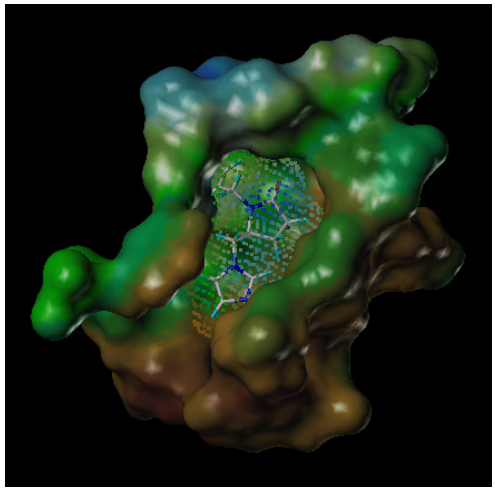
Key words: Rational drug-design, docking



Drugs exert their biological activity by interacting with the active site of the receptor. When the active site belongs to the transmembrane part of the receptor, drug molecules were found to act with a two-step mechanism. First, the molecule is incorporated into the bilayer and then it is laterally diffused in the active site. At the active site the drug interacts with the receptor through specific physicochemical interactions and either blocks the activation of the receptor or triggers a cascade of enzymic reactions responsible for a biological response. The study of the physicochemical interactions between the drug and receptor (docking) can reveal the pharmacophore segments of the drug that

govern its bioactivity and their conformation in space. In addition, it can aid in the design of novel molecules that may exert more productive interactions.

Energy interaction of the antihyrpertensive MM1 in the sheath of human AT1 receptor determined with theoretical algorithms

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Cis-trans Isomerism in Peptides and Proteins: A Structural and Thermodynamic Investigation

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Key words: Peptides, proteins, *cis-trans* isomerism, structural and thermodynamic investigation

Cis-trans isomerism plays a significant role, in conformational-activity relationships in proteins and drugs. At least, one cis-peptide bond was observed, in 6.5% of x-ray protein structures (1). Also, some peptide agonists and antagonists that contain a proline residue were observed to bind on proteins, with a cis-proline conformation. In order to investigate the structural and thermodynamic origin of the cis-trans isomerism and the influence of the environment, the N-methylformamide (NMF) and the bulky N-tert-butylformamide (TBF), simple compounds that contain a peptide bond, were examined by Nuclear Magnetic Resonance (NMR) techniques, as a function of concentration and temperature. Furthermore, some model proline derivatives (AcProOH, AcProNHMe and the ACE inhibitor Captopril) were examined in various solvents and in aqueous solution of different pHs. The thermodynamic parameters: standard free energy (ΔG^0), enthalpy (ΔH^0) and entropy (ΔS^0) of cis-trans isomerism were calculated (2) for the compounds in all solvents. Dimerization was observed in apolar solvents, especially of the cis-form. In some cases, the thermodynamic parameters of the dimerization process were calculated, too. The results clearly show, that at room temperature, as the polarity of the solvent decreases, the cis-form is favored. Also, the existence of a bulky group in the vicinity of the peptide bond increases the percentage of the cis-form. This is in excellent agreement with the high resolution x-ray results in proteins, where cis-peptide bonds were observed mainly in the vicinity of phenylalanine, tyrosine and tryptophane residues (3).

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