SPECIAL ARTICLE

Basic Research in Pulmonology

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This is a review of the articles dealing with basic science published in recent issues of *Archivos de Bronconeumología*. Of particular interest with regard to chronic obstructive pulmonary disease were an article on extrapulmonary inflammation and oxidative stress and another on bronchial remodeling. The articles relating to asthma included a review on the use of drugs that block free immunoglobulin-E and an article about the contribution of experimental models to our knowledge of this disease. Two of the most interesting articles on the topic of lung cancer dealt with gene therapy and resistance to chemotherapy. Also notable were 2 studies that investigated ischemia-reperfusion injury. One evaluated tissue resistance to injury while the other analyzed the role played by interleukin-8 in this process. On the topic of pulmonary fibrosis, an article focused on potential biomarkers of progression and prognosis; others dealt with the contribution of experimental models to our understanding of this disorder and the fibrogenic role of transforming growth factor β. In the context of both sleep apnea syndrome and pulmonary infection, studies investigating the role of oxidative stress were published. Finally, 2 studies analyzed the diagnosis and treatment of tuberculosis and other pulmonary infections.

Key words: *Experimental models. Basic research. Molecular biology. Respiratory diseases.*

La investigación básica en neumología

Se han revisado los artículos relacionados con las ciencias básicas que se han publicado recientemente en ARCHIVOS DE BRONCONEUMOLOGÍA. Respecto de la enfermedad pulmonar obstructiva crónica, destacan los relacionados con el estrés oxidativo y la inflamación extrapulmonar, y un estudio sobre la remodelación bronquial. Los artículos acerca del asma se centraron en revisiones sobre el uso de fármacos que bloquean la inmunoglobulina E libre y sobre las aportaciones de los modelos experimentales de la enfermedad. Respecto del cáncer de pulmón, cabe mencionar 2 trabajos centrados en la genoterapia y las resistencias ante la quimioterapia. También destacan 2 estudios sobre la lesión por isquemia-reperfusión, que valoraron el tiempo de resistencia tisular ante esta noxa y el papel de la interleucina-8. En el campo de la fibrosis pulmonar se revisaron los potenciales biomarcadores de progresión y pronóstico, así como el papel de los modelos experimentales de la enfermedad, publicándose además un trabajo sobre el papel fibrogénico del factor transformador de crecimiento beta. Sobre el síndrome de apneas del sueño y las infecciones pulmonares se publicaron sendos estudios acerca del papel del estrés oxidativo. Finalmente, 2 trabajos de investigación analizaron el diagnóstico y tratamiento de la tuberculosis y otras infecciones pulmonares.

Palabras clave: *Modelos experimentales. Investigación básica. Biología molecular. Enfermedades respiratorias.*

Introduction

The biomedical sciences advance thanks to the cooperation between clinical research and basic science. It is this second field of activity that aims to go more deeply into the mechanisms and factors involved both in disease and in the processes like aging that, though physiologic, have undesirable consequences. Ideally, the knowledge derived from basic biomedical research should be transferable to clinical practice, as its ultimate objective is to improve the diagnosis, management, and treatment of patients; it is for this purpose that society makes significant resources available to investigators. However, the results of basic research are at times somewhat removed from their practical application, or are not directed towards this, leading to controversy regarding their relevance and utility. This aim of this paper was to review the basic research articles published recently in *Archivos de Bronconeumología*. Because of the specific characteristics of the journal and its editorial policy, the transfer of knowledge is a major feature of all those articles. This review has been organized according to the different pathological processes that affect the respiratory apparatus.

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Chronic Obstructive Pulmonary Disease and Bronchial Asthma

Chronic obstructive pulmonary disease (COPD) is multidimensional, having features that range from airway damage and remodeling to inflammation, autoimmune mechanisms, and extrapulmonary disease.[1,2] In recent years, increasing importance has been given to systemic components, in particular muscle dysfunction,[3] which has recently been identified as an independent predictive factor of mortality.[4] The causes of this muscle dysfunction are unclear, but they appear to be related to a loss of lean mass, and include factors such as a poor physical condition secondary to a reduction in physical activity and the presence of systemic inflammation and oxidative stress.[5] In an interesting study, Morlà and coworkers[6] investigated the nitrosative modification of a key enzyme in skeletal muscle function: sarcoplasmic-endoplasmic reticulum Ca^{2+} adenosine triphosphatase 2 (SERCA2). They used samples from the quadriceps of both normal-weight and underweight patients with COPD. The samples were processed by Western blotting, which provides a semiquantitative approximation of the concentration of certain proteins in a sample. Immunoprecipitation with an antinitrotyrosine antibody identified tyrosine-nitrated proteins. The authors found that SERCA2 concentrations were lower in underweight patients compared to those with a normal weight, and that in underweight patients the results correlated with the concentration of inducible nitric oxide synthase. This last enzyme participates directly in the production of nitric oxide, which is a potent vasodilator, is involved in muscle growth, and promotes muscle contraction.[7] However, nitric oxide is also able to react with the superoxide anion (a highly reactive oxygen species) to produce peroxynitrite, which is also a powerful oxidant and cause of tissue damage. On the same subject, it is important to mention the authors' second finding: they observed tyrosine nitration of SERCA2 in underweight patients, indicating the presence of nitrosative stress.

Attention should also be drawn to an interesting article by Izquierdo and coworkers,[8] experts in chronic respiratory disease.[9] These authors investigated the systemic inflammatory response in the 2 classic phenotypes of COPD: emphysematous and predominantly bronchitic. They used the carbon monoxide diffusing capacity to differentiate between the phenotypes as this is a classic marker of pulmonary emphysema. In addition to a number of serum markers, the authors studied 3 inflammatory markers in exhaled air: interleukin (IL) 8, a potent neutrophil chemotactic factor that induces the expression of integrins by these cells and their adherence to other cells; 8-isoprostane, a marker of lipid peroxidation; and leukotriene B_4, which is also a chemotactic factor and stimulates leukocyte adherence. They found that the concentrations of the first 2 markers were lower in patients with a predominantly emphysematous phenotype. Although higher numbers of neutrophils were found in the blood tests from patients with COPD than in the control subjects, the results in the 2 phenotypes were similar. In addition, elevated blood levels of IL-8 were observed in patients with emphysema, whereas higher fibrinogen levels were found in those with the bronchitic phenotype. The authors concluded that both the inflammation and the oxidative stress are less intense in the lungs of emphysematous patients, in contrast with the more marked systemic involvement found in this phenotype.

Also relevant to chronic lung disease, there was an important study by Avilés and coworkers[10] on markers of bronchial remodeling in smokers. Those authors, who have previously published interesting studies on primary cultures of bronchial cells and analysis of the protein profile in respiratory secretions,[11,12] here focused on the initial phases of the disease and the early alterations caused by smoking. Specifically, they looked at the cellularity and the concentrations of both metalloproteinase (MMP) 9 and its inhibitor, tissue inhibitor of metalloproteinase (TIMP) 1, in sputum samples from smokers without chronic obstruction, patients with COPD, and healthy individuals. MMP-9 is a collagenase-type enzyme that regulates homoeostasis of the extracellular matrix.[13] It has been suggested that an imbalance between the proteases and their inhibitors in the lung could play a role in the progression and severity of COPD.[14] In the study mentioned above, the authors found that MMP-9 concentrations were already elevated in smokers, although the increase was even greater in patients with COPD. They concluded that even in the early stages, changes occur in the airways of smokers that lead to subsequent remodeling and that this will have functional repercussions manifest as COPD.

With regard to asthma, it is a classic respiratory disease in which there have been major advances in the understanding of its pathophysiology and therapy in recent decades, improving the clinical management of patients. A series of studies by Cabrera-Navarro[15-17] is of particular importance in the area of therapy as they provide a review of the basis for the actions of omalizumab, a monoclonal antibody that acts on the allergic reaction by blocking free immunoglobulin E.[18] This immunoglobulin is thus unable to bind to its cell receptors, inactivating the inflammatory cascade whatever the specific allergen. Other interesting actions of omalizumab are that it interferes with the expression of basophil membrane receptors and that it reduces eosinophil infiltration and the expression of their humoral products in the airway.[19,20] Its main inconvenience is its high price, and current recommendations are that it should be reserved for patients with severe asthma and a poor response to conventional treatment.

An interesting editorial by Ramós-Barnón,[21] describing the advances that have been made in the understanding of the pathophysiology of asthma thanks to basic research, also stands out in the literature of *Archivos de Bronconeumología* during the period of this review. The author underlines the importance of this disorder and the limitations of data obtained directly from patients. Experimental models of asthma, mainly murine models, have enabled some of these limitations to be circumvented, as it has been possible to induce allergic sensitization, bronchial inflammation and remodeling, the early and late allergic responses to bronchial challenge with allergens, and hyperreactivity to cholinergic agonists in these models.[22,23] In addition, as in many other diseases, it has been possible to obtain

relevant transgenic animals, enabling the role of certain proinflammatory substances in the initiation and perpetuation of the condition to be studied. However, as always occurs with these models, there are limitations when extrapolating their results to humans. The current challenge is to increase our understanding both of the adaptive features of the immune system and its role in the initiation and perpetuation of the asthmatic response, as well as of the mechanisms underlying tissue remodeling; in addition, the factors that have led to the increasing prevalence of the disease need to be explored. There is no doubt that experimental models can help to achieve these objectives.

Lung Cancer

This is one of the respiratory diseases with the highest prevalence and health care cost,[24] and it also has a major impact on how the specialties of pulmonology and thoracic surgery are viewed. Unfortunately, only surgical treatment is curative and, despite the recent advances in chemotherapy, only a transitory improvement in the quality of life has been achieved, with a delay in the deterioration and death of the patient.[25] A particularly worrying subject is resistance to chemotherapy, which can be innate or acquired.[26] One of the most common mechanisms of resistance is the fall in the intracellular concentration of the drug, whether through transport out of the cell, sequestration in vesicles, or changes in cell transport. Transport out of the cell through the membrane appears to be mediated by a series of proteins called multidrug resistance (MDR) proteins,[27] some of which are situated on the cell membrane (for example, multidrug resistance-associated protein [MRP] and P-glycoprotein [Pgp]) and others in the cytoplasm (for example, lung resistance protein [LRP]) or, to be more specific, in the so-called cytoplasmic vaults (ovoid capsular particles). Paredes and coworkers[28] have studied the expression of different MDR proteins in tumor samples from patients with lung cancer, and the relationship between this expression and clinical resistance. For this purpose, they took surgical or bronchoscopic samples from patients with lung cancer and performed immunohistochemical assays to detect Pgp (also called MDR1), MRP1, and LRP. The protein most commonly expressed was LRP, although coexpression was also a common finding. Only small groups of patients did not express any of the proteins studied. The level of expression did not correlate with age, sex, or characteristics of the tumor, but it did correlate with the response to chemotherapy, particularly in the case of Pgp or coexpression of various proteins. The authors confirmed that MDR proteins are present in a large number of tumors and that they can help us understand resistance to chemotherapy.

For their part, Rodrigo-Garzón and coworkers,[29] whose group focuses their attention on the diagnosis and treatment of lung cancer,[30,31] published an interesting article in which they used an experimental model of the disease to test gene therapy with vectors (defective recombinant adenovirus) or cell lines (transduced, syngeneic dendritic cells) carrying the gene for thymidine kinase or IL-12. In that model, these promising treatments were able to reduce tumor size in all cases.

Ischemia-Reperfusion Injury and Lung Transplant

The reduction or absence of blood flow, often followed by reperfusion of the previously ischemic area, is one of the most common causes of structural and functional lesions in many tissues. This type of lesion develops in myocardial ischemia/myocardial infarction,[32] ischemic cerebral infarcts,[33] pulmonary embolism,[34] and organ transplant. In addition, ischemia-reperfusion injury is an important cause of early morbidity and mortality after lung transplant.[35] However, the margin of time that a tissue is able to survive without adequate perfusion is not accurately known, although it is thought to be around 6 to 8 hours.[35,36] Santana-Rodríguez and coworkers,[37] in an excellent study, investigated the effects of prolonged ischemia and the subsequent restoration of blood flow in the transplanted lung. They used a murine experimental model of unilateral lung transplant, with ischemia maintained for variable periods (up to 10 hours) and the subsequent sacrifice of the animals. No differences were observed between the different groups with respect to the clinical signs of early rejection of the transplanted organ; nor were histological differences found. Their results indicate that it is likely that tissue resistance time to ischemia-reperfusion injury is relatively prolonged and exceeds what is currently accepted, at least in unilateral lung transplant.

In another study on the same subject of the transitory reduction of blood flow to lung tissue, Matilla and coworkers[38] analyzed the molecular mechanisms of ischemia-reperfusion injury, the pathogenesis of which is thought to involve both cellular and molecular inflammatory elements.[39] Specifically, Matilla and coworkers looked at the messenger RNA expression for IL-8 in the lung and its relationship with any histological changes in an experimental model of ischemia-reperfusion injury. Ischemia alone or ischemia-reperfusion with different ischemic times and in different lung lobes were reproduced in this model. It should be remembered that IL-8 is a potent promoter of polymorphonuclear cell movement from the blood into tissues, where these cells release mediators that can be harmful. In addition, IL-8 promotes cell degranulation and oxidative stress,[40] which, in turn, increases expression of the cytokine itself. Using a conventional polymerase chain reaction, the authors found that IL-8 expression increased during the first hour of ischemia and then remained at high levels, even during the subsequent reperfusion, with a second peak at 2 hours. In this phase, there was an early and persistent rise in the number of polymorphonuclear cells in the lung tissue, associated with edema, vascular congestion, and thickening of the interalveolar septa. The authors concluded that there must be a relationship between the local rise in IL-8 concentrations during ischemia and the subsequent appearance of tissue leukocytes during reperfusion; this would suggest that measurement of IL-8 concentrations could be useful in predicting the outcome of lung transplants and that there might also be useful therapeutic possibilities for IL-8 inhibitors.

Pulmonary Fibrosis

This is a fascinating disease in which we are discovering ever more elements involved its pathogenesis and clinical course.[41-43] However, treatment continues to be based on steroids and, in certain cases, chemotherapy. Recently, promising results have been found with antioxidant drugs and pneumocyte transplantation[44] in experimental models of the disease.

In an interesting review, Acosta[45] analyzed the compelling subject of prognostic biomarkers in this disease. The need for such markers arises from the fact that small functional or clinical variations are difficult to interpret and that the most reliable indicators of clinical course are histological and therefore difficult to obtain. Both radiology in expert hands and biological markers could help to resolve this problem, but no markers are clearly defined at present. The most prominent of those proposed is KL-6, a high molecular weight glycoprotein produced by damaged pneumocytes. Its concentrations may be increased in the bronchoalveolar lavage fluid from patients with idiopathic interstitial fibrosis,[46] although it is not totally specific and the concentrations do not appear to have a clear correlation with prognosis. In second place are the MMPs (also mentioned above, in the section on COPD and asthma), proteins secreted by a number of cell types into the extracellular matrix, where they regulate protein exchange. As has already been seen, their activity is regulated by tissue inhibitors (TIMPs). It is believed that the MMPs are involved in the initiation and subsequent progression of the fibrotic process due to their interactions with various cytokines, such as growth transforming factor (TGF) β and tumor necrosis factor α . It has also been suggested that imbalances between MMPs and TIMPs could play a role in fibrotic disease.[47] A third candidate is monocyte chemotactic protein, secreted by macrophages and alveolar and endothelial cells; it is relatively specifically raised in the bronchoalveolar lavage of patients with idiopathic fibrosis. In addition, this marker appears to indicate the response or lack of response to steroid treatment.[48] Lung surfactant proteins A and D (known respectively as SP-A and SP-D) have been related to changes in the extracellular matrix and fibroblast proliferation. It has been reported that raised plasma values of SP-D are predictive of an accelerated deterioration of the disease and poorer survival.[49,50] Among the cellular keratins, cytokeratin fragment 19 (CYFRA 21-1) has been found in raised concentrations in the plasma of patients with idiopathic fibrosis, and this marker could be useful in the prognosis of the disease.[51] However, as it is a nonspecific indicator of alveolar injury and remodeling, elevated concentrations may also be observed in other diseases. TGF-β, mentioned above, is a cytokine that is essential to tissue repair, but its overexpression may lead to fibrosis.[52,53] Raised concentrations have also been detected in the serum of patients with idiopathic interstitial fibrosis, and there is a reduction in the levels after treatment with steroids.[54] Finally, the role that this important fibrinogenic mediator plays in fibrosis has been evaluated in a study published in *Archivos de Bronconeumología*[55]; raised plasma concentrations of TGF-β were detected in patients with the disease, although it was not possible to establish a prognostic value for this biomarker.

In another review in this journal, Molina-Molina and coworkers[56] analyzed the different experimental models of pulmonary fibrosis, justified by the similarity of the fibrotic response between different animal species. Particularly important were those models that focus on the study of cell death, those looking at the synthesis and regulation of fibrogenic and antifibrogenic elements, and also those that evaluated possible new treatments. The majority of the models used small rodents, for their ease of handling and low cost; the fibrotic reaction was induced in the lungs by instillation of irritant substances (bleomycin, amiodarone, etc) using various routes or by irradiation of the lung tissue.[57-59] The bleomycin model was able to reproduce many of the histological elements of interstitial pulmonary fibrosis and has therefore been used widely in the evaluation of cellular lesions and damage to the extracellular matrix,[60] the mechanisms of action of various cytokines and growth factors,[61] and the genetic background that could favor the onset of disease.[62] Amiodarone can also be useful in inducing fibrosis[63] that is very similar to the fibrosis that develops in humans treated with this drug. Likewise, the inhalation of particles such as silica, asbestos, cobalt, cadmium chloride, or paraquat is able to induce pulmonary inflammation and fibrosis; in some of these models this is of the granulomatous type, very useful for studying macrophage behavior.[64] Irradiation can also be used to induce pulmonary fibrosis, although the equipment necessary for this model is more complex and requires specific precautions. Models with genetically modified animals can be very useful for studying patterns of susceptibility to fibrogenesis. These models may involve multiple genetic modifications, with an altered or absent expression of various proteins,[65] which is of particular interest as it appears that fibrosis is a polygenic condition in humans. In vitro models are also available to help us toward a better understanding of the behavior of certain cellular agents involved in fibrosis and their response to various substances.[66] The most important information that has come recently from experimental models refers both to the pathophysiology of the disease (specifically, the role played by epithelial cells together with the better-known role of fibroblasts and myoblasts, and the involvement of profibrotic factors)[52] and to the response to certain treatments (for example, interferon, pirfenidone, N-acetylcysteine, and bosentan).

Respiratory Sleep Disorders

The interest in sleep disorders has increased exponentially in the past decade, with society becoming ever more aware of their prevalence and social and health impact. Although the mechanical causes of the disorder and many of its clinical consequences are relatively well known, the causative and subsequent cellular mechanisms are still unclear. Among the factors that have been implicated in the development of the cardiovascular alterations that are associated with sleep apnea-hypopnea syndrome (SAHS) is oxidative stress. This occurs when

there is an imbalance between the production of free radicals and the defense mechanisms, leading to changes in proteins (both structural and enzymatic), in lipids, and in DNA itself, with important implications for cell function and viability.[67,68] Hernández and coworkers[69] published a study on this subject in which they evaluated the effect of the use of continuous positive airway pressure (CPAP), the classic treatment for SAHS, on the presence of systemic oxidative stress, measured in that study using the concentration of malondialdehyde (an indicator of lipid peroxidation in particular). Before treatment, the indices of oxidative stress, were raised in patients with SAHS, confirming the findings of other groups.[70] The authors' most interesting finding was the observation of a significant fall in oxidative stress after 3 months of CPAP treatment. This was confirmed recently by others[71] and indicates that CPAP counteracts some of the mechanisms involved in the cardiovascular impact of SAHS. It may not be possible to extrapolate this to all the systemic effects of the disease, as it appears that oxidative stress persists in the skeletal muscles after treatment with CPAP.[72]

Respiratory Tract Infections

Tuberculosis continues to be a major health problem[73] and has re-emerged in developed countries due to factors related to globalization. Because of the complexity of the treatments, eradication policies have been ineffective, leading to a search for therapeutic vaccines aimed at eradication of all mycobacteria, including so-called latent ones, which are able to survive without causing disease and without being detected by the immune system. Cardona and Amat[74] published an interesting review of the origin and development of the vaccine known as RUTI. The initial premise was that it should be able to immunize the host against bacilli both in the multiplication phase and in the latency phase. Another factor the developers took into account was that the objective of antibiotic treatment in latent infection aims to eliminate organisms that are actively multiplying or that attempt to enter this phase, as well as to eliminate the inflammatory load in the area of the lesion. However, such treatment also depresses immune competence, as it leaves concentrations of the bacillary population at such low levels that they do not stimulate an immune response.[75] For this reason, a vaccine for administration after chemotherapy would be of great interest, and it would be even better if this vaccine could reduce the duration of chemotherapy. These requirements are satisfied by the RUTI vaccine, which is created from biotransformed cellular fragments of the bacillus included into liposomes, permitting its administration after a shorter period of chemotherapy, and which is able to destroy the latent bacillus.[76] The mechanism of action of the RUTI vaccine is the induction of a potent polyantigenic response, balanced between T helper (T_H) cells (T_H1, T_H2, and T_H3) and an intense antibody production. It is highly effective in murine models[77] and is already being developed for future use in humans.

Determining the organism that is causing a lung infection in order to start the most appropriate treatment often presents problems. The techniques used most commonly include blood and sputum cultures, but they have certain limitations, such as delayed diagnosis and problems of specificity and/or sensitivity, and this has led to a search for alternatives. Of particular importance among the alternatives developed is the detection of antigens in easily accessible biological samples, such as urine. Based on the high concentration of antigens in this fluid and the absence of technical interference from other substances, this technique is useful for the immunologic identification of microorganisms such as *Legionella pneumophila* and *Streptococcus pneumoniae*. A paper by Molinos[78] reviewed the utility of these methods for the detection of antigenuria. In the case of the pneumococcus, the assays usually detect the capsular polysaccharide; after the disappointing results with techniques such as counterimmunoelectrophoresis, latex agglutination, coagglutination, and enzyme immunoassay, detection has been greatly facilitated by the development of immunochromatographic membrane assays. This technique has good sensitivity and very high specificity. In addition, the result can be obtained within only 15 minutes. There are problems, however, as positivity is not altered by successful treatment and can persist for a month after the infection.[79] It can be helpful at the time of deciding both the antibiotic to be administered and whether or not to admit a patient. Furthermore, it should be taken into account that bacteremic pneumococcal pneumonia, a condition in which the sensitivity of antigen detection reaches 85%, has a high morbidity and mortality. With respect to *L pneumophila*, diagnosis is usually based on tedious methods with a relatively low sensitivity (for example, direct and indirect immunofluorescence, sputum culture). Great advances have also now been made in the detection of the antigens of this microorganism in urine. Enzyme immunoassay techniques are now available[80] and there is the above-mentioned membrane immunochromatography. Although the yield of these 2 techniques is similar, the second provides a more rapid diagnosis (in only 15 minutes) and requires less instrumental infrastructure. Moreover, it appears that sensitivity can be almost doubled if the urine is concentrated previously, and the specificity is also very high.[81] The antigen identification technique for pneumococcus is indicated in community-acquired pneumonia in order to prescribe a specific treatment, whereas the suspicion of *Legionella* infection or the presence of an epidemic of legionellosis would indicate the use of the specific antigen for this organism.

Finally, in their excellent research article, Romero and coworkers[82] focus on the role of oxidative stress in tissue damage and in the inflammatory process associated with lesions. They make particular reference to lung infections, specifically bacterial infection, to evaluate whether the indices of oxidative stress in exhaled air could reflect the situation within the lung. In samples of exhaled air, the authors measured the concentrations of nitrite (NO_2) and nitrate (NO_3) (both of which are derivatives of NO, which is able to induce the peroxynitrite, a powerful radical), myeloperoxidase (which converts hydrogen peroxide into a more powerful oxidant: hypochlorous acid), and 8-

isoprostane (a good marker of molecular transformations due to lipid peroxidation). Samples were collected from healthy subjects and from patients with various infectious diseases: multilobar pneumonia without mechanical ventilation, severe pneumonia requiring mechanical ventilation, and COPD exacerbated by infection. All the patient groups presented raised levels of the above-mentioned markers, with no significant differences between the various conditions. The authors concluded that it was possible to obtain an indication of the state of pulmonary oxidative stress from a sample of exhaled air, although studies are required in order to relate the findings in this type of sample to changes in lung tissue.

Conclusions

In summary, in recent years there has been a significant presence of original and review articles on the basic sciences in *Archivos de Bronconeumología*, including an appreciation of the transfer of such knowledge to clinical practice. This reflects a general tendency in the biomedical literature and coincides with the marked development in technology and in our understanding of basic science over the past 2 decades.

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