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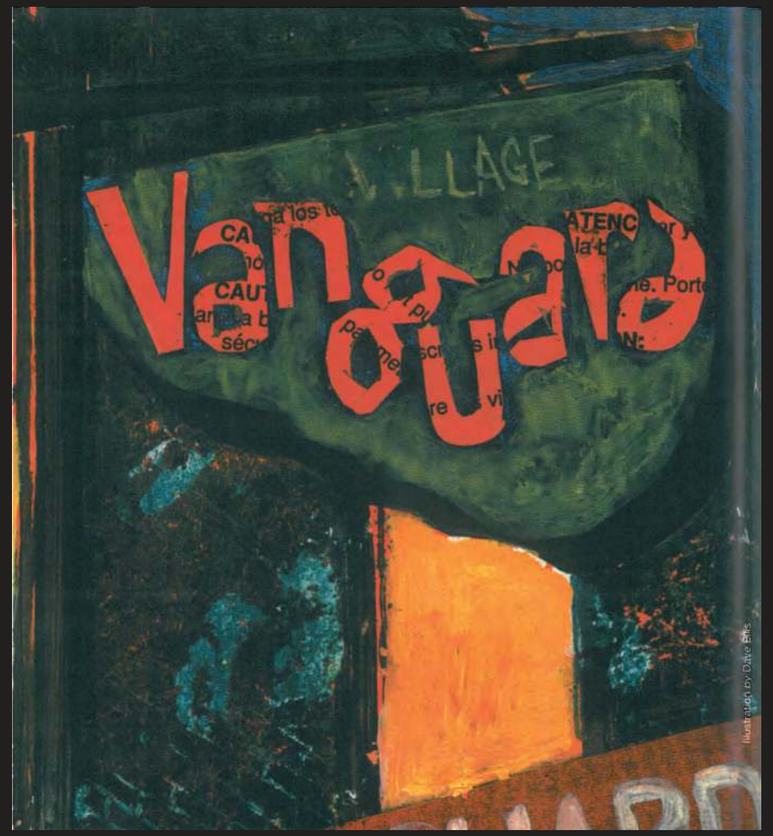

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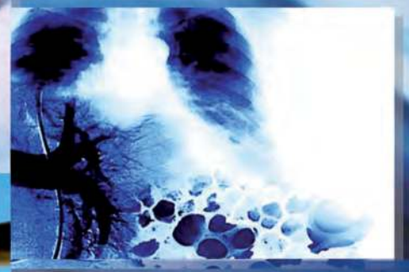

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Call for Scientific Research Proposals 2014

Chiesi Foundation Onlus invites scientists and researchers to submit proposals for high level scientific research projects in the following scientific domain:

Pneumology and chronic respiratory diseases management.

The topics proposed should aim to enlarge the knowledge in the medical community and in health care-providers on the interaction between environmental and lifestyle factors and the whole respiratory tract and to foster the communication of scientific messages to the medical community and the general population.

Proposals that significantly advance scientific understanding in the aforementioned domain via highly productive collaborative teams with multi-disciplinary expertise are strongly encouraged.

In particular, this Call seeks proposals aimed at reaching one the of the following specific objectives:

Objective 1. To describe the effect of lifestyle factors (e.g. diet, exercise) on chronic respiratory diseases, such as for example childhood overweight/obesity and asthma in children or physical activity in smokers with/without COPD.

Objective 2. To study the interaction between indoor/outdoor pollution and the human lung, including effects on small airways and predisposition to airway diseases (e.g. asthma).

Objective 3. To develop single reproducible and validated methods (lung function, cell biology, imaging, etc) or their combination for the diagnosis of small airways disease.

Researchers, whatever specific topic they focus on, are required to devise a communication strategy, by developing effective and adaptable tools for improving the diffusion of scientific result(s) and message(s) from specialists (e.g. pulmonologists, allergologists) through general practitioners to the general population.

The deadline for the submission of the projects is October 1st, 2014 and the approved proposals will be granted access to Chiesi Foundation Onlus resources from 2015 onwards.

The beneficiaries of the grants will be asked to provide detailed reports and annual summary, demonstrating sufficient progress toward the stated goals.

Supporting documents can be found on *www.chiesifoundation.org.*

For information write to *info@chiesifoundation.org.*

The Village Vanguard,
located at the 178,
Seventh Avenue South, NY

About the cover

The Village Vanguard

The Village Vanguard is a small jazz club located in New York City's Greenwich Village. Officially opened by Max Gordon in April 1935, it was intended to be a forum for poets and artists, as well as a venue for musical performances. "There wasn't much music for the first couple of years- Max said- just a piano player", such as Leonard Bernstein, and writers like Jack Kerouac. Hence, in the thirties and forties, patrons of the club would hear poetry and folk music. However, on Saturday afternoons, jazz sessions started to make an appearance.

"For fifty cents at the door or something like that, you could hear all the greatest jazz musicians at the Vanguard" says Max Gordon's wife, Lorraine, who survived Max in 1989. During those years, Roy Eldridge, Lester Young, Ben Webster, Sidney Bechet, Mary Lou Williams and many other high-caliber jazz artists and their "small groups" performed there.

The Village was also a place to showcase a new artist, like Thelonious Monk. He was introduced to Max Gordon by his future wife Lorraine. She insisted that the Village let the pianist play, and so on September 14th, 1948, Monk debuted to the bafflement of critics and the public alike. His lack of success continued for some time, and only later did Monk get recognition for his brilliant talent as a player and composer admired the world over.

In 1957, Miles Davis, Horace Silver, Gerry Mulligan, The Modern Jazz Quartet, Jimmy Giuffré, Charlie Mingus, and Stan Getz, to name only a few, played at the Vanguard. That same year, legendary recording sessions began as well. The first to record was Sonny Rollins on November 3rd, 1957. During his recordings, Sonny, a jazz tenor saxophonist, made three LPs considered today to be the avant-garde of hard-bop.

In 1961, John Coltrane and Bill Evans made live recordings. Coltrane's album, *Live at the Village Vanguard*, contains five tracks chosen from more than twenty recording made over four nights at the Vanguard. Bill Evans (*Sunday at the Village Vanguard*) was flanked by Scott LaFaro and Paul Motian and the trio was considered to be seminal to modern jazz. Evans went back to the Vanguard after LaFaro's accidental death in 1980, three months before his own passing.

In later years, Art Pepper (1977), Tommy Flanagan (1986), Wynton Marsalis (1999) and many others had their names on albums which were recorded live at the Village. *"Live at the Village Vanguard"* still today represents a seal of quality and excellence.

Mythical places and epigenetics

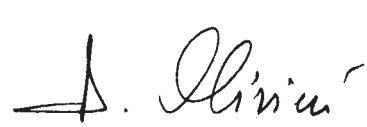
When Jazz lovers walk into places like the Village Vanguard, the Fillmore East in New York City or the Fillmore West in San Francisco, they immediately feel the vibe inside. These clubs conjure up memories of the best performances by their idols. Similarly, classical music and opera aficionados feel the passion when they go to La Scala in Milan, Carnegie Hall in New York City or the Teatro Regio in Parma to hear their favorite pieces interpreted by wonderful artists.

Respiratory medicine also has its mythical places, linked to a single person or an entire research group. Who does not know of the Cardio Vascular Research Institute (CVRI) in San Francisco, or the Brompton Hospital in London, or the Pasteur Institutes in Lille or Paris?

What makes a research facility legendary? The great scientists, the research methodology, or the air one breathes in that environment? It is difficult to pinpoint a single factor, but it is probably all of these things well measured and mixed together ("stirred, not shaken"). *The names of the* "Giants" *of respiratory medicine come to mind easily due to their individual talents. Chest recently dedicated an issue to celebrate the most notable ones. Are these people unique because they are geniuses, or geniuses because they found the right environment that fostered their talents to create and develop research ideas?*

An important observation must be considered; when a student (often not yet a researcher) is accepted at one of these prestigious institutes, they usually succeed with their research project. Whether they come from Italy, Japan or some less fortunate land, their project, which may be well established or modified in itinere, *is usually concluded to the great satisfaction of the student and host institution. Well after completing his or her stage, the memory and imprinting of that unique experience will stick forever in the student's mind. A researcher feels great pride in saying he or she is a member of the* old boys (girls) *club of a famous institute.*

In other words, the student's experience is a wonderful example of epigenetics. The influence of the environment around us is undeniable but its expression is unpredictable and varies in relation to the genetic baggage of each single researcher.



Idiopathic pulmonary fibrosis: definition and clinical picture

Stefania Cerri
Center for Rare Lung Disease, Department of Oncology, Hematology and Respiratory Diseases, University Hospital of Modena, Modena (Italy)

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of diffuse parenchymal lung disease of unknown aetiology. Certainly IPF is the most frequent and the most lethal among all idiopathic interstitial lung diseases, with an estimated median survival of 2.4 years from diagnosis. It affects adults with a higher prevalence in the 6th and 7th decade and a slight predominance of male gender. Smoking history is reported in the majority of cases. Upon exclusion of secondary causes, IPF can be diagnosed by the recognition of a definite usual interstitial pneumonia pattern (UIP) on high-resolution computed tomography (HRCT) of the chest, or by specific combinations of UIP patterns on HRCT and surgical lung biopsy. Multidisciplinary discussion is strongly recommended in the evaluation of suspected IPF.

Patients usually present with non-specific symptoms such as progressive dyspnoea, primarily on exertion, and chronic dry cough lasting from months to years prior to clinical observation. Digital clubbing may be present. At chest auscultation, bilateral basal inspiratory crackles (so-called "Velcro" crackles) are typical findings. Lung physiology will reveal a restrictive ventilator defect and a reduction of lung diffusion capacity for CO. Given the non-specific presentation, patients might have received alternative diagnoses and, as a consequence, delayed referral to specialized centres for proper management is common.

Natural history of the disease can vary and it is largely unpredictable at the time of diagnosis. IPF is believed to have a chronic course, characterized by progressive impairment of respiratory symptoms and lung function. However, with increased knowledge in this disease, subsets of patients with relatively stable or slowly progressive disease have been recognized. On the other end, some patient may experience a rapidly progressive clinical course leading to the death within months after diagnosis. Furthermore, acute exacerbations of IPF of unknown cause represent unpredictable events that can occur at any time during the course of the disease, that lead to severe acute deterioration of clinical conditions and are associated with

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high mortality. Comorbidities such as pulmonary arterial hypertension, cardiovascular disease and gastro-oesophageal reflux might have an impact on survival, although main causes of death in IPF patients are respiratory (i.e. disease progression or exacerbation).

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Stefania Cerri *graduated in 2003 from Medical School of University of Eastern Piedmont (Italy) with Full Marks and Honors; in 2007 she completed the fellowship program at the Respiratory Disease Clinic of the University Hospital of Modena. Thereafter Dr. Cerri entered the PhD program in Clinical and Experimental Medicine at the University of Modena and Reggio Emilia where she developed an interest in translational research in two main areas of interest, i.e. tuberculosis and pulmonary rare disease, under the mentorship of Prof. Luca Richeldi. She spent more than two years at the Division of Pulmonary and Critical Care Medicine of the Oregon Health and Science University, Portland, Oregon (United States), working with Prof. David Lewinsohn on innate and adaptive immune responses against M. tuberculosis in the lung and in the peripheral blood. Since 2010, Dr. Cerri has been working as Respiratory Disease Specialist and Postdoctoral Research Associate at the Center for Rare Lung Diseases. Dr. Cerri has developed an interest in understanding the pathogenesis of interstitial lung diseases, and in 2011, she received a Young Investigator Award from the Italian Ministry of Health for a project investigating mesenchymal progenitor cells as biomarkers in idiopathic pulmonary fibrosis. Dr. Cerri is also working as co-investigator in several research projects carried out by the Center for Rare Lung Disease at University Hospital of Modena and has established fruitful collaboration with international centers such as the Woolcock Institute of Medical Research at the University of Sydney (Australia) and the Interstitial Lung Disease Program at UCSF (United States). She has co-authored several publications in peer-reviewed journals.*

Mechanism of idiopathic pulmonary fibrosis

Melanie Königshoff
Comprehensive Pneumology Center (CPC)
Helmotz Zentrum, Munich (Germany)

***Melanie Königshoff**, MD, PhD is head of a Young Investigator Group at the Comprehensive Pneumology Center (CPC) at the Helmholtz Zentrum in Munich. Dr. Königshoff aims to decipher the pathogenesis of chronic lung disease and explores novel routes to initiate lung repair and regeneration. Her research has a translational approach combining patient studies, development of preclinical human lung tissue models, as well as animal models and cell biology. Recently, Dr. Königshoff has been awarded with the prestigious ERC Starting Grant. Dr. Königshoff is a Faculty Member of the German Center of Lung Research (DZL) and an active member of the European Respiratory Society (ERS) and the American Thoracic Society (ATS). She is currently the Program Chair of the ATS Respiratory Cell and Molecular Biology Assembly. Dr. Königshoff is actively involved in MD/PhD training and the director of the CPC International Graduate Program "Lung Biology and Disease". She published over 35 original peer-reviewed articles with more than 800 citations.*

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IPF is a progressive and devastating lung disease characterized by cellular injury and altered homeostasis in the peripheral lung, leading to excessive accumulation of extracellular matrix (ECM), and ultimately, loss of lung function. While genetic determinants, occupational, or environmental exposures, such as smoking, pollutants, viral infections, or aging have been suggested as risk factors for IPF, its origin and onset remains to be clearly elucidated. IPF currently affects up to 150.000 patients and 200.000 patients in Europe and the US, respectively. The incidence of IPF has continuously increased in past decades in the Western world (UK data show an increase of 35% from 2000-2008). Despite emerging advances in our understanding of its pathogenesis in the past years, IPF to-date still exhibits a 50% mortality 3-5 years after diagnosis. Since currently available therapies show only limited efficacy, lung transplantation remains the only therapeutic intervention with a known survival benefit for IPF patients. While several novel therapeutic targets have entered clinical trials in past years (e.g. triple kinase inhibitors, integrin antibodies, CTGF antibodies), important key questions in IPF remain to be further elucidated.

Currently, the onset of IPF is thought to involve perpetuated microinjuries to the alveolar epithelium, leading to dysregulation of cellular homoeostasis in the alveolar epithelial–mesenchymal unit, reactivation of developmental signaling pathways (e.g. TGF- or Wnt), induction of cell dysfunction and death, formation of scar tissue, and, finally, distortion of lung homoeostasis and lung structure. This lecture will highlight the current knowledge and discuss recent findings that have been implicated into IPF development and progression.

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Management of idiopathic pulmonary fibrosis

Athol Wells
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Royal Brompton Hospital (RBH)
London (UK)

Before the millennium, idiopathic pulmonary fibrosis (IPF) was viewed as an "inflammatory/fibrotic disorder", with inflammation preceding and leading to fibrosis. It must now be acknowledged that this view was not founded on clinical or scientific observations but reflected the fact that anti-inflammatory and immunosuppressive therapies were the only treatments available to clinicians. The use of IPF treatment protocols consisting of high dose corticosteroids, often in combination with cyclophosphamide or azathioprine, amounted to a litany of failure. With the reclassification of the idiopathic interstitial pneumonias in 2002, it became apparent that the minority of "IPF" patients responding to this treatment approach had disorders other than IPF. In the 2011 ATS/ERS/JRS/ALAT guidelines for the diagnosis and management of IPF, high dose corticosteroid therapy and combination corticosteroid/immunosuppressive treatment received strong negative recommendations. Triple therapy (low dose corticosteroid therapy, azathioprine and N-acetyl cysteine) had beneficial effects in retarding disease progression in the IFIGENIA trial. However, in the recent placebo-controlled PANTHER study, this regimen was associated with a striking excess of hospital admissions and deaths.

The PANTHER study has been interpreted in a woefully over-simplistic fashion. Corticosteroid therapy was given in high doses during the first 16 weeks (an average of approximately 25mg daily in a population with a mean age of nearly 70) and the excess of adverse events was confined to this period. The PANTHER study can be viewed as a four month trial of high dose corticosteroids, azathioprine and N acetyl cysteine, with the findings confirming the already current view that this approach is actively damaging. Sadly, the findings have led to the assumption that all forms of immunomodulation are harmful in IPF, a view which is entirely unsubstantiated by current data. Immune dysregulation is apparent in a large patient subset with IPF and it remains entirely possible that alternative less aggressive forms of immunomodulation might eventually be shown to be beneficial. In acute exacerba-

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tions of IPF, high dose corticosteroid therapy continues to rescue a minority of patients in whom it is likely that there is a major component of organizing pneumonia (i.e. subacute damage, as opposed to diffuse alveolar damage).

Despite these caveats, it is now accepted that the chronic inflammatory model of IPF is a failed model, at least as regards documented treatment effects in chornic disease proigression. IPF is now conceptualised as an "epithelial/fibrotic" disorder with exciting treatment benefits now demonstrated with the antifibrotic agents, pirfenidone and nintedanib. Key phase three data, released in detail a week before this presentation, will be reviewed. Unequivocal effects in retarding disease progression and, in the case of pirfenidone, significant all-cause mortality benefits will be discussed. Importantly, both agents are highly pleiotropic, with down-regulation of a variety of fibrogenetic pathways and a component of anti-inflammatory activity.

Neither therapy can be viewed as transformational. On average, 30-40% of progression is prevented and there is a 40% to 50% reduction in all-cause mortality over 12-18 months with the use of pirfenidone. It can be argued that we have a "best current therapy" and that placebo-controlled IPF trials are now unethical. But there is clearly a need to find ways to amplify the benefits. The dilemma we face is whether combination regimens might be synergistic or whether the future focus should be on personalised medicine with pathway signal informing the use of specific treatments in patient sub-groups.

eRn

Athol Wells is a Professor of Respiratory Medicine and Head of the Interstitial Lung Disease Unit at the Royal Brompton Hospital (RBH), London, UK. He graduated from the University of Otago in New Zealand and after completing specialist training, also in New Zealand, he came to RBH as a research fellow in interstitial lung disease and bronchiectasis where he completed an MD. He returned to New Zealand to a specialist post for five years before moving back to the UK in 1999. He is a fellow of the Royal College of Physicians, a fellow of the Royal College of Radiologists and a member of the Fleischner Society. His research interests include structure/ function work with HRCT and pulmonary function tests (for staging and monitoring), pulmonary vascular disease in interstitial lung disease, and accurate phenotyping for a large variety of scientific/genetic studies. H e was the chairman of the BTS group which recently revised guidelines for the diagnosis and management of interstitial lung diseases and a co-chairman for the ATS/ERS initiative to revise the classification of the idiopathic interstitial pneumonias. Over the last decade, he given many presentations at major symposia in leading international meetings. He is an author /co-author of over 200 peer reviewed articles (published or "in press") and over 100 chapters, review articles and editorials. H e is an editor/co-editor of four books, covering sarcoidosis, interstitial lung diseases, lung involvement in connective tissue disease and key clinical problems in radiology.

Inflammation in Asthma, COPD and ACOS

Peter J. Barnes
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ERS President 2013/14

***Peter Barnes** is Margaret-Turner Warwick Professor of Medicine at the National Heart and Lung Institute, Head of Respiratory Medicine at Imperial College and Honorary Consultant Physician at Royal Brompton Hospital, London. He qualified at Cambridge and Oxford Universities (first class honours) and was appointed to his present post in 1987. He has published over 1000 peer-review papers on asthma, COPD and related topics (h-index 145) and has written or edited over 50 books. He is the 7th most highly cited researcher in the world, has been the most highly cited clinical scientist in Europe and the most highly cited respiratory researcher in the world over the last 20 years. He was elected a Fellow of the Royal Society in 2007, the first respi-*

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Both asthma and COPD involve chronic inflammation of the respiratory tract that leads to airflow limitation and respiratory symptoms and it has been argued that they are both different manifestations of the same disease process (Dutch hypothesis). However, in the majority of patients there are marked differences in the inflammatory process in these diseases, with involvement of different cell, mediators, different consequences and different response to treatment. Some patients with COPD also have features of asthma, however as both diseases may coexist in the same patient but relatively little is known about this asthma-COPD overlap syndrome (ACOS)..
Asthma is a disease of variable bronchoconstriction due to the intermittent and triggered release of several bronchoconstrictor mediators. Structural changes (airway remodelling) also occur with time, including subepithelial fibrosis (present even in very mild disease but not seen in COPD), airway smooth muscle hypertrophy and hyperplasia, angiogenesis, mucus hyperplasia and airway fibrosis. Asthma usually involves large airways but in more severe disease extends to involve small airways. By contrast, COPD involves mainly small airways and lung parenchyma (destruction). Airway obstruction is due to fibrosis and thickening of small airways and loss of alveolar attachments so that airways close on expiration trapping air and leading to hyperinflation and exertional dyspnoea.
Both asthma and COPD involve many different inflammatory cells types, with the consequent release of multiple different and differing mediators. In asthma there is an activation of surface mast cells, which release several bronchoconstrictor mediators such as histamine, leukotriene D_4 and prostaglandin D_2. There is usually an infiltration of eosinophils, orchestrated by $CD4^+$ Th2 cells, which release the Th2 cytokines IL-4, IL-5. IL-9 and IL-13. IL-4 and IL-13 stimulate B cells to release IgE to sensitise mast cells which are enhanced by IL-9 and stem cell factor. Dendritic cells play a key role in asthma and regulate Th2 cells via the chemokine CCL17 acting on CXCR4. Thymus stromal lymphopoeitin (TSLP), is

a key upstream cytokine released by epithelial cells that results in activation of dendritic cells. In addition to acquired immune cells there are also innate immune cells that are regulated by epithelial mediators, such as IL-33 and IL-25. In asthma ILC2 cells predominate and release IL-4, IL-5 and IL-13, independent of allergen. In COPD there is a different pattern of inflammation, with recruitment of neutrophils, increased numbers of macrophages and a predominance of $CD8^+$ Tc1 cells as well as Th1 cells. Regulatory T cells (T_{reg}) may be defective in asthma and COPD. Mast cells do not seem to play a key role in COPD. Dendritic cells are probably important in COPD, are found within lymphoid follicles and provide a link between innate and acquired immunity. There is fibrosis around small airways and TGF- is believed to play an important role, but smooth muscle hypertrophy is not seen to the same extent as in asthma. There is alveolar wall destruction (emphysema) with loss of elastic fibres due to an imbalance between elastases (particularly MMP9) and antiproteases; $CD8^+$ cells may also contribute to alveolar wall destruction via apoptosis of alveolar wall cells. There is also a .loss of small airways (terminal bronchioles) even in mild disease. Several transcription factors regulate the inflammation in asthma and COPD. NF- B is activated in asthma and COPD and regulates the expression of multiple inflammatory genes. In asthma GATA-3 in Th2 and ILC2 cells plays a key role in orchestrating allergic inflammation.

Although there are marked differences between mild asthma and COPD, patients with severe asthma have many features similar to COPD. For example there is an increase in neutrophils in the airways, there may be activation of CD8+ and Th1 cells and mediators such as TNF- and CXCL8 become predominant. There is also an increase in oxidative stress as in COPD and this may contribute to the poor responsiveness to corticosteroids. Asthmatics who smoke also have increased neutrophilic inflammation, oxidative stress and lose steroid responsiveness. IL-17 may be an important mediator of neutrophil inflammation in asthma and COPD and is released from Th17 cells that secrete predominantly and are regulated by IL-23. Some patients with COPD have increased eosinophils and share characteristics with asthmatics, including increased reversibility and response to corticosteroids. ACOS may be due to the simultaneous presence of asthma and COPD or may represent a variant of COPD.

eRn

ratory researcher for over 150 years. He is currently a member of the Scientific Committee of global guidelines on asthma (GINA) and COPD (GOLD). He also serves on the Editorial Board of over 30 journals and is currently an Associate Editor of American Journal of Respiratory and Critical Care Medicine, Chest, Journal of COPD and respiratory Editor of PLoS Medicine. He has given several prestigious lectures, including the Amberson Lecture at the American Thoracic Society, the Sadoul Lecture at the European Respiratory Society and the Croonian Lecture at the Royal College of Physicians, London. He has been received honorary degrees from the Universities of Ferrara (Italy), Athens (Greece), Tampere (Finland), Leuven (Belgium) and Maastricht (Netherlands). He is a NIHR Senior Investigator and was elected a Master Fellow of the American College of Chest Physicians and a member of Academia Europaea in 2012. He is currently President of the European Respiratory Society. He co-founded an Imperial spin-out company RespiVert, which was acquired by Johnson & Johnson and has developed novel inhaled treatments for COPD and severe asthma.

Cross-talk between inflammation and fibrosis in asthma and COPD

Klaus F. Rabe
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Asthma and COPD share a number of clinical features but there are marked differences in the pattern of inflammation in the respiratory tract, with different inflammatory cells, mediators and response to therapy. Inflammation in asthma predominantly involves the larger airways while in COPD it involves predominantly small airways and the lung parenchyma. However, patients with chronic and severe asthma have airway inflammation that is more similar to that seen in individuals with COPD with an apparent convergence of cytokine networks resulting in variable signs of fibrosis. Specifically, cytokines implicated in airway inflammation can promote differentiation and survival of inflammatory cells or result in proliferation and/or activation of structural cells, contributing to airway remodeling including fibrosis. TGF-β represents a family of pleiotropic cytokines that play several roles in asthma and COPD. TGF-β is a growth factor that, amongst other functions, induces the proliferation of fibroblasts and airway smooth muscle cells, deposition of ECM, and epithelial repair. There is increased expression of TGF-β1, particularly in eosinophils in asthmatic airways, and this has been associated with subepithelial fibrosis. Increased expression of TGF-β2 has also been reported in patients with severe asthma. In COPD there is increased expression of TGF- by airway epithelial cells from small airways and macrophages. The fibrotic effects of TGF-β are largely mediated via increased secretion of connective tissue growth factor (CTGF), which shows increased expression in microarray analysis of COPD lungs. GM-CSF is secreted predominantly by macrophages, epithelial cells, and T cells in response to inflammatory stimuli and plays a role in the differentiation and survival of inflammatory cells such as neutrophils, eosinophils, and macrophages and has been implicated in asthma and COPD. Its receptor has an β-chain specific for GM-CSF and a β-chain that is part of the receptors for IL-3 and IL-5. Airway epithelial cells of asthmatic patients express GM-CSF and in COPD, GM-CSF is released by alveolar macrophages and may be important for increased survival of neutrophils and macrophages in

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the airways. Increased concentrations of GM-CSF in BAL fluid of COPD patients, particularly during exacerbations, are correlated with the increased numbers of neutrophils. Neurotrophins are cytokines that play an important role in the function, proliferation, and survival of autonomic Nerve growth factor (NGF) may be produced by mast cells, lymphocytes, macrophages, and eosinophils as well as structural cells, such as epithelial cells, fibroblasts, and airway smooth muscle cells. Although neurotrophins have predominant effects on neuronal cells, they can also act as growth factors for inflammatory cells, such as mast cells, as well as increasing chemotaxis and survival of eosinophils. Finally, VEGF plays an important role in regulating the growth of new vessels and vascular leakage in asthmatic airways. Increased expression of VEGF and VEGF receptors is correlated with increased vascularity in asthmatic airways. In contrast, VEGF concentrations are reduced in the lungs and sputum of patients with COPD. Collectively, there is good evidence that inflammatory changes in asthma and COPD form the basis of fibrotic changes throughout the lung, although with different pathological patterns. For some of the pathways involved there are by now specific inhibitors available with the potential of modulating processes of airway remodeling.

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Asthma-COPD Overlap Syndrome: the clinical implications

Globally, asthma and chronic obstructive pulmonary disease (COPD) are two prevalent disorders with a significant diseases burden and are, therefore, of major public health concern. In principle the two disorders have principally different risk factors, patterns of prevalence and incidence, pathology and physiology. The two diseases, however, can present with a significant overlap in clinical signs and symptoms, and can occur in identical age groups. In the sixties of the last century observational studies have led to postulate that the two disease entities are in fact identical forms of lung affections, and the presenting differences were marginalized by suggesting merely different risk factors leading to very comparable clinical syndromes. On the hand hand, allergic sensitization and on the other hand cigarette smoke. This theory, first formulated by Orie and commonly referred to as the ´The Dutch Hypothesis´ named this common disease entity

´CARA´ and this concept influenced for many years the medical system in The Netherlands and Belgium. With the broader use of inhaled corticosteroids, more intense research into the biology, immunology and pathology of asthma and COPD and through a broader knowledge base on their prevalence and outcomes, the two syndromes were later clearly recognized as two different disease entities with different approaches to management and (pharmaco)therapy. While this differentiation and separation appears reasonable and based on well conducted pathological and physiological studies, the clinical dilemma remains that in a numerically not further not defined group of patients a clear distinction cannot be made and there are indeed individuals that share definable characteristics of both disorders. Notably this verlap appears more prevalent in the older population. For the development of clinical practice guidelines the clinical overlap of asthma and COPD poses a dilemma, since commonly these documents try to clearly distinguish the two disorders and so far there has been little practical guidance how to systematically approach management in case of significant overlap. In the meantime, both GINA and GOLD have developed a written strategy to address the putative asthma – COPD overlap syndrome, or ACOS, to facilitate the development of a common standard. While this document may address a common clinical problem, it does theoretically carry the risk of oversimplification and might even counteract the professional campaigning to implement broader lung function testing, and – ultimately – might lead to an uncritical use of inhaled medication, inhaled corticosteroids in particular.

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New insights in severe asthma

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Asthma management is focused on achieving total asthma control in two domains. First is current control, where the patient is asymptomatic all of the time, has normal lung function and no limitations in activities. The second in minimizing future risk of severe exacerbations, accelerated decline in lung function and avoiding side effects from medications.

Currently available treatment, particularly with inhaled corticosteroids (ICS) with or without long-acting inhaled β_2-agonists (LABA) can achieve good asthma control in many patients. However, repeated studies have indicated that most asthma patients do not achieve total control. The commonest reason for this is poor adherence with asthma treatment. Some patients, however, will not achieve asthma control, even with maximal doses of currently available therapy, perhaps as many as 10%. These patients are considered to have severe refractory asthma. It has become evident that severe refractory asthma consists of a very heterogeneous population of patients. In addition, many diseases can masquerade as severe asthma. An accurate diagnosis and careful phenotyping is needed to identify which newer treatments may benefit an individual patient.

Recently approved treatment approaches for patients with severe refractory asthma include bronchial thermoplasty and adding the muscarinic antagonist, toitropium to ICS/LABA combination and a third line therapy. In addition, a number of experimental treatments are being developed. An example of the necessity to phenotype patients with severe refractory asthma has been the development of monoclonal antibodies (hMab) directed against interleukin (IL)-5. Two antibodies have been developed (mepolizumab and relizumab), neither of which showed benefit in a non-selected cohort of patients with difficult-to-treat asthma; however, when studied in patients with a persisting airway eosinophilia, these treatments have been shown to reduce asthma exacerbations and improve lung function. The use of induced sputum was essential to identify these patients with a persisting airway eosinophilia, despite optimal treatment. Similarly, a hMab directed against IL-13 significantly improved lung function in patients

with difficult-to-control asthma, but only in those with an elevated serum periostin (a protein produced by airway epithelial cells after stimulation with IL-13). Also, a hMab directed against the IL-4Rα, which is the common component of the receptor for IL-4 and IL-13, is showing promise in patients with elevated blood eosinophil counts. Other treatment approaches are targeting patients with a persisting airway neutrophilia using a CXCR2 (the receptor for IL-8, GRO-α and GRO-β) antagonist, or the addition of macrolide antibiotics.

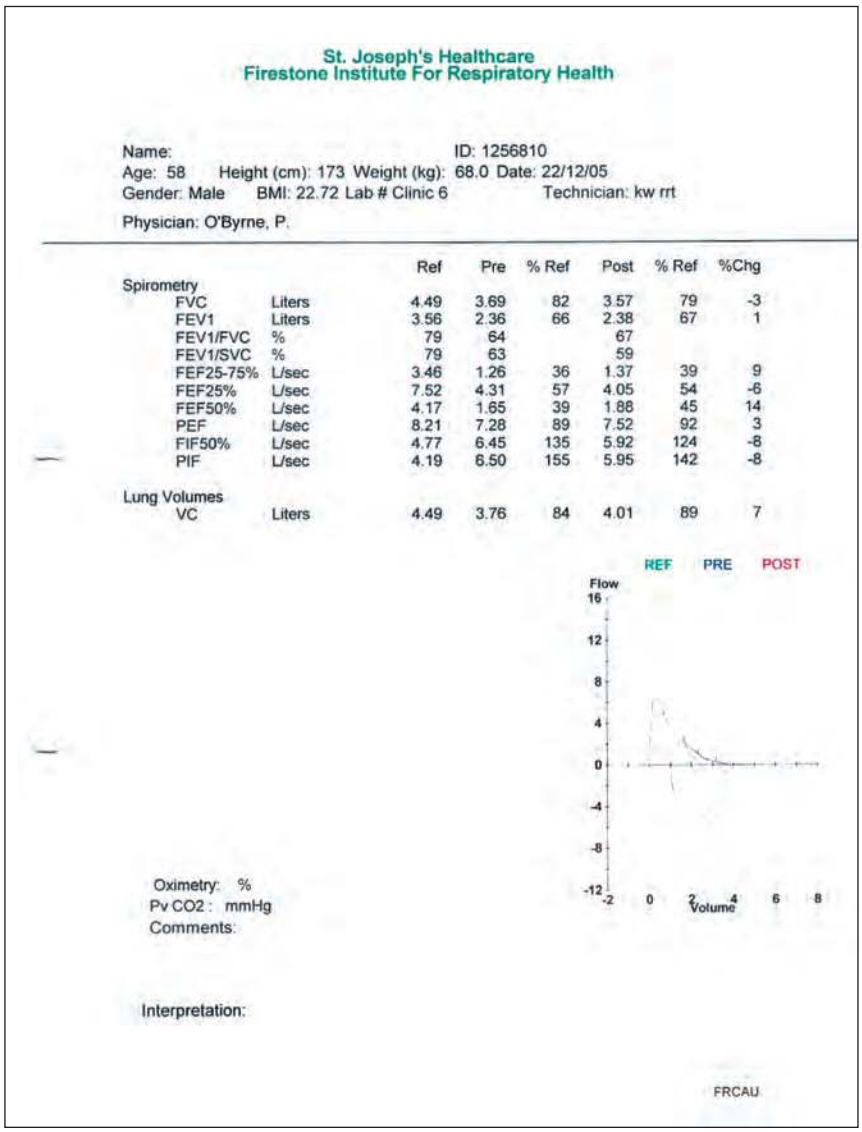
It is likely that all new treatments for severe refractory asthma will need efforts at phenotyping to identify populations of patients likely to benefit, as this group of patients have such heterogeneous mechanisms causing their severe disease.

eRn

Case Report: Severe asthma and an atypical lung infection

A 58 year old male was referred to the Severe Asthma Clinic in December 2005 for assessment of a diagnosis of allergic bronchopulmonary aspergillosis (ABPA). The patient had a history of asthma since his teenage years, and this had been controlled until 4 years before. Since that time, he had experienced daily asthma symptoms requiring rescue medication use, intractable cough and sputum production, nocturnal symptoms and treatment for severe asthma exacerbations with oral corticosteroids (prednisone) on average 4 times per year. He denied any symptoms of rhino-sinusitis or gastroesophageal reflux. He was being treated with fluticasone/salmeterol 500/50mcg twice daily, salbutamol as needed and intermittent courses of prednisone. He was on no other medications and denied any known allergies. He had previously been treated with montelukast and theophylline added to maintenance ICS/LABA treatment, but these had provided no benefit and they were discontinued. A sputum culture had previously demonstrated moderate growth of Aspergillus Fumagatus, but no bacteria.

The patient's other past history was unremarkable. He worked as a hospital administrator and was a lifelong non-smoker. There was a strong family history of asthma, with his mother, brother and sister all treated for asthma. He had no pets in the home.



St. Joseph's Healthcare
Firestone Institute For Respiratory Health

Name: ID: 1256810
Age: 58 Height (cm): 173 Weight (kg): 68.0 Date: 22/12/05
Gender: Male BMI: 22.72 Lab # Clinic 6 Technician: kw rrt
Physician: O'Byrne, P.

		Ref	Pre	% Ref	Post	% Ref	%Chg
Spirometry							
FVC	Liters	4.49	3.69	82	3.57	79	-3
FEV1	Liters	3.56	2.36	66	2.38	67	1
FEV1/FVC	%	79	64		67		
FEV1/SVC	%	79	63		59		
FEF25-75%	L/sec	3.46	1.26	36	1.37	39	9
FEF25%	L/sec	7.52	4.31	57	4.05	54	-6
FEF50%	L/sec	4.17	1.65	39	1.88	45	14
PEF	L/sec	8.21	7.28	89	7.52	92	3
FIF50%	L/sec	4.77	6.45	135	5.92	124	-8
PIF	L/sec	4.19	6.50	155	5.95	142	-8
Lung Volumes							
VC	Liters	4.49	3.76	84	4.01	89	7

Oximetry: %
Pv CO2 : mmHg
Comments:

Interpretation:

FRCAU

Figure 1 - Spirometry testing at time of first visit. The patient has moderate airflow obstruction. There was no improvement after bronchodilator.

Investigations

Spirometry showed and FEV_1/VC of 2.36/3.69L (predicted normal 3.56/4.49), with no improvement after bronchodilator (Figure 1); all other pulmonary function tests were normal. His blood count was normal, except for a circulating eosinophil count of 460. Induced sputum showed a normal cell count, but with 48% eosinophils. His total serum IgE was 4480 IU/ml. Skin testing to a panel of 18

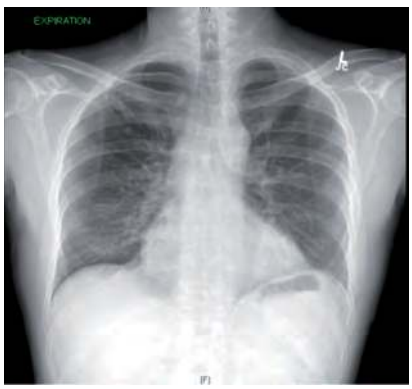


Figure 2 - CXR showing several nodular densities in the right upper lobe

common environmental allergens (including aspergillus) was all negative. Aspergillus precipitins were also negative.

A chest X-ray showed nodular densities in the right upper lobe (Figure 2). A high resolution chest CT scan was completed. This demonstrated several pulmonary nodules in the right upper lobe with cavitation in one of these (Figure 3). There was no central bronchiectasis suggestive of ABPA. Tuberculin skin test and a vasculitis screen were negative.

A fiberoptic bronchoscopy was conducted. This demonstrated widespread airway inflammation, but no masses. A bronchoalveolar lavage (BAL) was performed in the right upper lobe. The BAL cultures grew mycobacterium avium complex (MAC), but not mycobacterium tuberculosis.

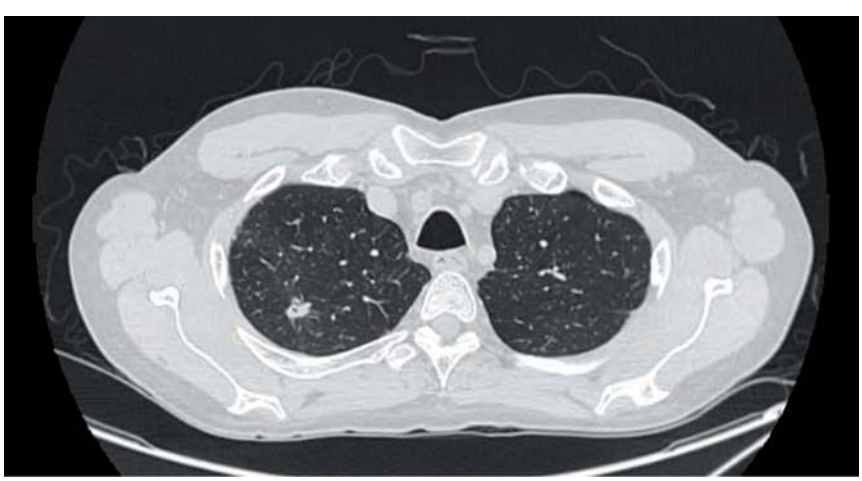


Figure 3 - Slice of the Chest CT scan showing a cavitating nodular density in the right upper lobe

Treatment

The patient was treated in March 2006 with triple therapy with ethambutol, rifampin and clarithromycin daily for 1 year. He was also switched to budesonide/formoterol 200/6 mcg as maintenance and rescue treatment.

Progress

He returned to clinic in June 2006 and his cough and sputum production had almost completely resolved. He was still requiring rescue medication most days and almost every night. His FEV_1/VC was unchanged at 2.2/4.1L. He required courses of prednisone for severe asthma exacerbations in November and December 2006.

The patient was started on the anti-IgE monoclonal a omalizumab in December 2006, because of the high serum IgE, although his skin tests did not identify any environmental sensitizations. He was much improved by June 2007, not requiring daily rescue medication use. Since that time he has had well and he has not experienced a severe asthma exacerbation between then and 2014. His spirometry has not changed. His CXR is now normal.

Discussion

This man presented with severe refractory asthma, a blood and air-

way eosinophilia and a very high serum IgE. The initial referral was for the investigation of possible ABPA, which has an increased prevalence in patients with severe asthma and patients with cystic fibrosis, and treatment of which with anti-fungals has been shown to improve asthma control (1). He has right upper lobe nodules, one of which was cavitating. He did not have ABPA. His BAL cultures grew mycobacterium avium complex and he was treated with triple therapy for 1 year, which resolved his intractable cough and sputum production, but did not control his asthma. The addition of omalizumab provided asthma symptomatic control and reduced the risk of severe asthma exacerbations, even though the patient was not sensitized to any obvious environmental allergens.

A recent case-control study has examined the association of atypical mycobacterial infection and severe asthma (2). These investigators identified 22 patients with severe refractory asthma and atypical mycobacterial lung infections. The patients were infected with either MAC or Mycobacterium xenopi. These patients were older than matched control, with more severe airflow obstruction. Their asthma was more severe and they required more frequent courses of oral corticosteroids. It is unclear whether the oral corticosteroids increased the risk of the mycobacterial infection, as occurs in older asthmatic patients for Mycobacrerium tuberculosis (3). Ten of the 22 cases were treated with antibiotics, and 7 demonstrated clinical improvement in their asthma control. The authors concluded that atypical mycobacterial infection can be associated with asthma and should be considered in severe refractory disease, especially in older individuals with more severe airflow obstruction and greater exposure to corticosteroids.

Omalizumab is established as a treatment option for patients with severe allergic asthma (4), and has been demonstrated to reduce the risks of severe asthma exacerbations (5), also in patients already treated with ICS/LABA combination therapy (6). The current patients had serum IgE levels higher than normally recommended for this treatment approach and also had no identifiable environmental allergy. Omalizumab has not been shown to consistently improve pulmonary function. This treatment was started as nothing else was providing asthma control. The patient's asthma control markedly improved and he has not experienced a severe asthma exacerbation in 7 years since starting omalizumab therapy. There have been discussions with the patients about stopping the omalizumab, but the patient has declined to do so.

eRn

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A, B, C, D: are GOLD strategy applicable in clinical practice?

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Global Initiative for Chronic Obstructive Lung Disease (GOLD) was formed 15 years ago to improve the management and prevention of COPD. Awareness of COPD has always been a key objective of GOLD.

However, the main aim of GOLD has always been to provide guidance for the diagnosis and management of COPD. In 2001, the GOLD program released its first consensus report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD* (1); this document was revised in 2006 (2) and 2011 (3). This document is updated annually. The GOLD document is a global document and for that reason alone should not be regarded as a guideline. Although an overall strategy may have value globally, actual guidelines will have to differ. There is bound to be different requirements for the contents of guidelines for e.g. Europe and North America than for developing countries with far less economical power to spend on management of non-communicable disease such as COPD. The strategy document provides guidance on principles and drug classes to be applied. National or regional guidelines can choose to use aspects of it but will need to modify guidance, choice of drugs and not least organisation of care to their local needs.

The GOLD 2011 revision

For the 2011 revision of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) the severity staging (GOLD stages 1-4) that had been put in place ever since the original strategy document in 2001 was abandoned in favour of a classification using a broader assessment. The new assessment is meant to be a meaningful way of classifying patients that can be directly translated into treatment, non-pharmacological as well as pharmacological (3). The downside to this is that it can no longer serve as a prognostic tool or index as the old GOLD stages could. However, there are several indices better than the GOLD stages; e.g., the BODE index (4) or the ADO index (5).

The new assessment combines symptoms, spirometry (forced expiratory volume in 1 second, FEV_1) and history of exacerbations, and

classifies patients into one of four groups, GOLD groups A, B, C and D. There were two main reasons for the reclassification. First, it was considered that staging by FEV_1 only was insufficient. Numerous studies have shown that as lung function is too simple a marker of a complex disease like COPD. Other measures such as breathlessness, mucus hypersecretion, exercise tolerance and exacerbation frequency add to the overall impact of the disease and its prognosis. On the other hand, GOLD Stages 1-4 were well-known and it would be a waste not to utilise this categorisation of airflow limitation. Secondly, although the GOLD stages 1-4 were very useful for communicating and describing patients, several trials had not used these stages for inclusion criteria and they therefore became less useful for COPD management. In fact, landmark studies like TORCH (6) and UPLIFT (7) had used other upper limits for FEV_1 than those generally advocated by GOLD. Finally, it was believed that an assessment that could be used for directing treatment was more important than a severity classification.

The main features of COPD that can be impacted on with treatment are overall symptoms – i.e. health status – and risk of exacerbations. It can be argued that the far most disabling symptom of COPD is breathlessness and that this symptom alone could be used for assessment. After significant deliberation, the novel assessment based on symptoms and risk of exacerbations was proposed. Thus, the GOLD A-D classification is based on an assessment of symptoms and future risk of exacerbations, leading to the 4 groups: A - few symptoms & low risk, B – many symptoms & low risk, C – few symptoms & high risk, and D – many symptoms and high risk. For symptoms assessment, CAT (8) is preferred although mMRC evaluation of breathlessness can be a substitute. For risk assessment, FEV_1 (GOLD 3-4 vs. GOLD 1-2) and history of exacerbations are both included as markers of risk of future exacerbations (9 ,10); see Figure 1.

A number of issues were intensely discussed up to the launch of the GOLD 2011 revision. First, there was an argument as to whether GOLD should propose cut-points for the split in A-D; the argument against was that it was impossible to come up with firm recommandation, the argument in favour of cut-points was that without them the document was too abstract. Secondly, it was argued that comorbidities should be part of the assessment and classification of COPD. GOLD does recommend that comorbidities should be assessed regularly and in the 2011 revision a novel chapter on comorbidities was included. However, it was not seen possible – and perhaps not attractive either – to have a number of other diseases built into the classification of one disease.

The contents

In my biased view, the new assessment is simple and functional. Four GOLD groups are defined.

GOLD Group A patients have few symptoms and a low risk of exacerbations. Specific evidence for the effectiveness of pharmacologic treatments is not available for patients with FEV_1 >80% predicted (GOLD 1). However, GOLD recommends a short-acting bronchodilator as first choice based on its effect on lung function and breathlessness. Second choice is a combination of short-acting bronchodilators or the introduction of a long-acting bronchodilator. The evidence for this step-up is weak as is any evidence of effectiveness of rehabilitation in this patient group.

GOLD group B patients have more significant symptoms but still a low risk of exacerbations. Long-acting bronchodilators are recommended; GOLD has not found evidence to recommend one class of long-acting bronchodilators over another for initial treatment. Pulmonary rehabilitation should also be offered to this patient group. For patients with severe breathlessness, the second choice is a combination of long-acting bronchodilators despite limited evidence of efficacy on patient-related outcomes.

GOLD group C patients have few symptoms but a high risk of exacerbations. There has been doubt ads to the real existence of this group, but subsequent studies have shown that they do indeed exist; likely, many of these are not diagnosed, especially if they have few symptoms, few previous reported exacerbations but low FEV_1. GOLD recommends either a combination of inhaled corticosteroid/long-acting $beta_2$-agonist or a long-acting anticholinergic as first choice treatment. Group C patients should be offered rehabilitation if they have had serious exacerbations.

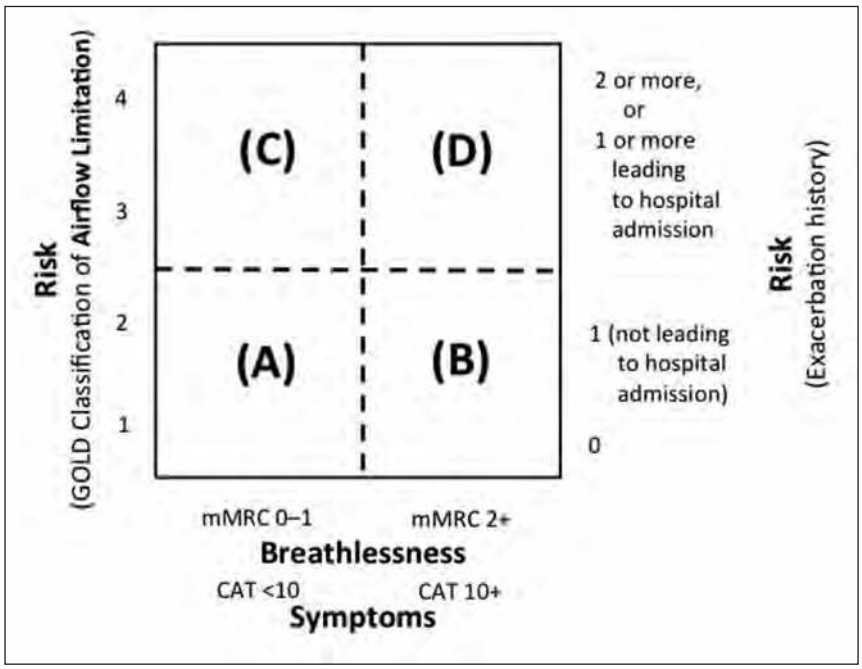

Figure 1 - Combined assessment using symptoms, FEV_1 and history of exacerbations. Reprinted with permission from GOLD.

GOLD group D patients have many symptoms and a high risk of exacerbations and these make up the

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large majority of patients seen by specialists and in hospital clinics. The rationale for the first choice of therapy is the same as that for patients in Group C, as reduction of exacerbation risk seems most important. As second choice a combination of all three classes of drugs (inhaled corticosteroid/long-acting beta$_2$-agonist/long-acting anticholinergic) is recommended, although there are conflicting findings concerning this treatment. It is also possible to add a phosphodiesterase4-inhibitor to the treatment chosen as first choice, provided the patient has chronic bronchitis. Group D patients should routinely be offered pulmonary rehabilitation.

Subsequent studies

Subsequent studies have taught us several things. First, the A-D classification can be implemented and patients can be categorised. In the initial wording, CAT and mMRC were proposed in parallel but not surprisingly the two measures will categorise patients differently (11, 12). This comes as no surprise; CAT is a short general health status measure whereas mMRC only focuses on breathlessness. Clearly, patients with very little shortness of breath but multiple other symptoms will score high on CAT and low on mMRC. There is a higher likelihood for patients to end up in B & C if CAT is used. This is unfortunate but unavoidable. In the square denoting A, B, C and D, we deliberately chose to have dotted line between the different GOLD groups as we wanted to highlight the concept rather than discuss in detail if an individual patient was in one group or another. In the real world, patients are seen by healthcare providers who will have to take the individual patient's presentation and complaints into account.

Distribution of patients is – again not surprisingly - very dependent on the population studied (13-15). In a study of a general population sample there will be far more Group A patients than D patients whereas the opposite is likely to be true if patients are selected from secondary or tertiary care. This is also what studies so far have shown. Interestingly, Groups C and D seem of similar sizes in studies reported from both a Danish general population sample and the ECLIPSE patient population.

The A-D grouping is not superior to 1-4 for prognosis (13-16), but that was not to be expected. As high-lighted earlier, the A-D groups were defined for the purpose of more patient-centered management and not for prognosis. When looking at what determined 'high risk of exacerbations' (i.e. being placed in Group C or D), it has turned out that more or less identical findings have come out of analyses to date. Risk of exacerbations in Groups C and D seems

highest if patients have both a history of frequent exacerbations and an FEV_1 less than 50% and lowest if patients have low FEV_1 only. This could potentially be used in future revisions of the GOLD Strategy document if a more detailed assessment of risk seems attractive – and it probably is as so much treatment is aimed at reducing risk.

Patients in Group B have a particular high risk of adverse comorbidity outcomes that should be taken into account (13). This relates in particular to cardiovascular disease outcomes but also cancer mortality is significantly higher in Group B (and in Group D) than in Groups A and C. In short, severe symptoms – not least breathlessness – in a COPD patient should warrant an even more extensive assessment of comorbidities.

GOLD A-D more complicated than 1-4?

The GOLD A-D classification has been criticised for being too complicated for practical purposes. This criticism comes mainly from pulmonary physicians as both internists and general practitioners are used too far more complicated algorithms; e.g., for risk assessment in ischaemic heart disease.

Conclusion

GOLD Groups A-D were developed to better classify patients based on symptoms and risk of exacerbations and to provide better management of patient with COPD. There will be different opinions as to the utility of the new GOLD classification but the 2011 revision has indeed sparked discussion that will be useful to the field of COPD. Most likely changes to subsequent updates and revisions will probably be in the assessment of risk and potentially by including comorbidities in the assessment. However, the new classification cannot be evaluated fully until clinical trials have evaluated how the new classification performs regarding treatment prediction compared to the old staging system.

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COPD case 1

62-year old man with known COPD, diagnosed 6 years earlier. Smoking history of 55 pack-years, "quit" in 2008 but occasionally smokes 2-3 cigarettes per day. Breathlessness when hurrying on level ground, remains physically active and does brisk walking for 30 minutes every day and visits the gym every week. He complains of a productive morning cough on a daily basis. He experiences 3-5 exacerbations every winter, almost always with increased cough, fatigue, purulent sputum and a temperature of 38-38.5°C. He is usually treated with 10 days of ampicillin & clavulanic acid and 5 days of prednisolone, 37.5 mg daily.
Spirometry shows post-bronchodilator FEV_1/FVC of 0.48 and FEV_1 of 53% of predicted normal. Body plethysmography reveals a RV of 120% of predicted normal and TLC 108% of predicted normal. 6 MWD is 410 meters.
His Dexa scan last year was normal and he has been referred to a cardiologist on suspicion of heart failure but had a normal Echo.
HRCT has shown mild emphysematous changes and areas with slightly thickened airway walls and minimal dilatation of peripheral bronchi, no obvious bronchiectasis.
Sputum culture during his last exacerbation showed significant growth of *Haemophilus influenza*, sensitive to ampicillin & clavulanic acid and ciprofloxacin but resistant to erythromycin.
His treatment consists of Tiotropium bromide 18 mcg in the HandiHaler once daily and Terbutalin 0.5 mg in the Turbuhaler for use when needed (takes it rarely). In addition, he takes simvastation 40 mg once daily because of a slightly elevated se-cholesterol.

His main concern is risk of continued exacerbations. What will you do?

COPD case 2

44-year old woman, diagnosed with COPD three years earlier. Had asthma as a child with symptoms disappearing when she was 12-13 years old. Still has seasonal rhinitis with known allergy to birch, verified by skin prick test. Parents and 2 siblings without atopy, her own two children have eczema and one has wheeze with airway infections. Smoking history of 35 pack-years, quit in 2010. Breathlessness when hurrying on level upstairs or when running. She complains of an occasional dry cough, also occurring at night. She has mild reflux symptoms, she has been offered PPI by her previous GP but she did not think her symptoms were severe enough to require medication.
She comes to see you during her third exacerbation this year. As usual it started with mild symptoms of a cold that within 2 days worsened with coughing up grey sputum, increased breathlessness and wheeze. Poor sleep quality. She has not measured her temperature.

Spirometry shows post-bronchodilator FEV_1/FVC of 0.63 and FEV_1 of 63% of predicted normal. Her chest x-ray is normal.
In clinic she has a normal temperature and an ECG showing sinus tachycardia with HR 104.
Six months ago you prescribed her Symbicort Forte (budesonide 320 mcg + formoterol 9 mcg) in the Turbuhaler twice daily. Two months ago you added Tiotropium bromide 18 mcg in the HandiHaler once daily but the patient has stopped taking it because of a dry mouth and joint pain. She takes Terbutalin 0.5 mg in the Turbuhaler 4-6 times daily. In addition, she takes paracetamol 1 g 3-4 times daily for joint pain.

She is concerned that her treatment is useless and she tells you that she is close to being fired from her office job because of sick leave. What will you do?

Jorgen Vestbo *was born in 1959 and graduated from the University of Copenhagen in 1984.*
He is job-sharing, working as a Professor of Respiratory Medicine in the Respiratory Research Group at University of Manchester, UK, and at the Department of Respiratory Medicine at Gentofte University Hospital / University of Copenhagen in Denmark.
His main research interests are epidemiology and clinical research in COPD. He has been involved in several large COPD trials such as The Copenhagen City Lung Study, TRISTAN, TORCH, SUMMIT and the Salford Lung Study, and he has been co-chairing the Steering Committee of the ECLIPSE study.
He has worked on the Scientific Committee of GOLD and was as committee chair responsible for the 2011 revision and subsequent updates. He is currently serving as vice president of the European Respiratory Society.

Prevention and management of exacerbation in COPD, asthma and asthma-COPD overlap syndrome: where do we stand?

Alberto Papi
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Both patients with asthma and those with COPD experience exacerbations of their disease. Exacerbations are similarly defined in both diseases as acute events characterized by an increase in symptoms from usual status that is sufficient to require a change in treatment. They are frequently triggered by infections of the respiratory tree and they are associated with quality of life impairment and increased healthcare utilisation. Exacerbations impact on the natural history and the progression of the disease as subjects experiencing frequent exacerbations show accelerated loss of lung function in both conditions. This raises the possibility that modifying the exacerbation rate may control the evolution of the disease.

International guidelines provide evidence-based recommendations for the identification, prevention and effective treatment of these acute episodes. The topics most recently debated in this field include the role of viral infections as triggers of exacerbations and the possibility of increasing antiviral immune response to effectively prevent/treat virus associated exacerbations. Similarly, the role and the mechanisms of bacterial infections in exacerbating these conditions have been extensively investigated. The efficacy of the antibiotic treatment of COPD exacerbation and of long term antibiotic prevention has been recently debated. Novel biological approaches targeting markers specifically associated with increased risk of exacerbations have been proposed in the last years and a number of randomized clinical trials are currently ongoing assessing the efficacy of inhibiting selective pathways/markers (e.g. eosino-philia) and of interfering with molecular mechanisms relevant to the development of exacerbations of asthma and COPD.

Asthma-COPD overlap syndrome (ACOS) is an entity recently introduced in international guidelines recommendations. It is characterized by fixed airflow limitation and by features shared with asthma and COPD. The information on the relevance/frequency of acute events in this condition is scarce and it is mainly obtained from small single-centre studies. No randomized clinical trial have been performed specifically in this pop-

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ulation. As a consequence, the evidence for the treatment and prevention of exacerbations in this population is indirect and is often extrapolated from overlapping conditions, either asthma or COPD. Original investigation is mandatory to provide supporting evidence for the treatment of this group of patients.

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Cognitive Impairment in Patients with COPD

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Chronic Obstructive Pulmonary Disease (COPD) is a progressive and partially reversible pathological condition of the respiratory system which can variably affect also cognition. The effects of other less severe chronic airway disorders on cognitive functioning still remain to be clarified. The aim of our research was to measure and compare the extent of cognitive deterioration in COPD subjects of different severity as well as in subjects with Chronic Non-Obstructive Bronchitis (CNOB) and in asymptomatic smokers (AS) of comparable age, and to relate the corresponding prevalence to several demographic and clinical variables, and to normal reference values.
Methods: a representative sample of 402 subjects (COPD n=229; CNOB n= 127, and AS n= 46, respectively) was investigated (personal and family history; lung function; measurement of Health

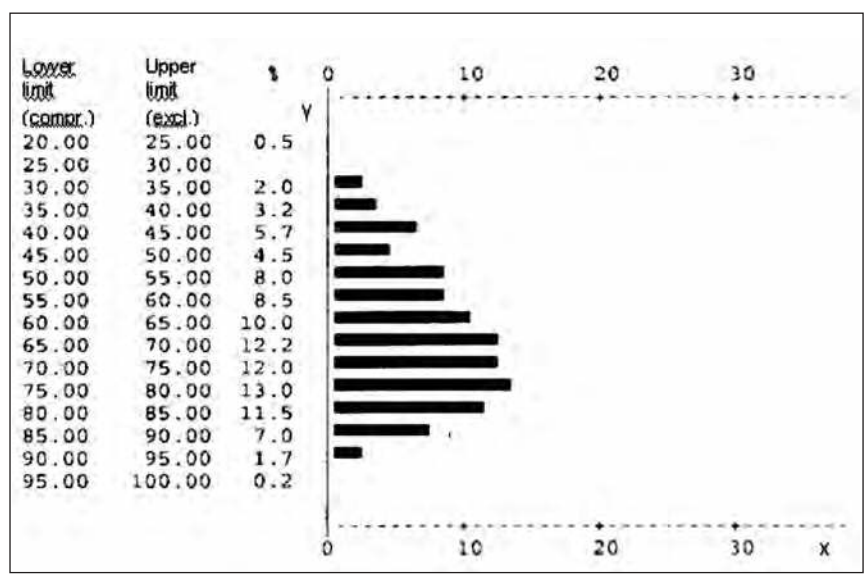

Figure 1 - Percentage distribution of age, ranging 20–100 years (intervals of 5 years)

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Table 1 - Main characteristics of the whole sample and of each cluster of subjects investigated.

	Whole sample n= 402	AS n=46	CNOB N=127	COPD n=229
males/females	274/128	32/14	84/43	158/71
ratio	2.1/1	2.2/1	2.0/1	2.2/1
age	65.6±15.1	50.6±11.3	62.2±15.7	70.5±12.9
smokers				
active	22.6%	100%	36.3%	16.6%
ex	63.7%	0%	40.9%	65.5%
never	13.7%	0%	22. 8%	17.9%
mean BMI	27.7±5.7	26.9±4.5	28.8±6.1	27.1±5.6
mean MRC score	2.0±1.2	1.1±0.8	1.7±1.2	2.4±1.1
mean CAT score	15.3±6.9	12.7±7.1	14.3±6.8	16.4±6.7
mean FEV1%pred.	68.4±29.5	100.0±15.2	87.6±26.2	54.9±23.6
mean FEV1/FVC	65.8±17.0	77.6±6.0	79.8±9.2	52.7±11.9
mean PaO2	71.6±11.8	81.5±6.1	73.4±12.1	69.5±11.3
mean PaCO2	42.3±9.7	38.3±7.7	40.8±7.5	43.5±10.6
comorbidities	64.7%	63.0%	64.6%	65.1%

Status – the CAT questionnaire, and of dyspnoea score – the MRC scale). The impairment of cognition was assessed by means of four validated psychometric questionnaires (such as: the MMSE; the

Table 2 - Normal limits and mean scores ± sd calculated for each psychometric test in each cluster of subjects, together with the prevalence of pathological scores for each psychometric test, and the level of statistical significance for comparisons among clusters (anova)

	Clock Drawing test (score)	% subjects with score ≤6	MMSE Test (score)	% subjects with score <24	Trial Making test A (sec)	% subjetcs with score ≥94 sec	Trial Making test B (sec)	% subjects with score ≥283 sec
Normal reference values	7-10		>27		<94		<283	
AS	9.2±0.5sd	0	28.6±1.0sd	0	76.3±19.0sd	0	164.3±58.9sd	2.2
CNOB	8.2±2.1sd	8.7	27.7±2.4sd	15.7	92.3±51.7sd	34.6	199.5±109.9sd	28.3
COPD	7.2±2.6sd *	16.6	26.9±3.1sd *	32.8	115.1±60.6sd *	49.3	236.2±111.1sd *	40.2
anova	* p<0.001		* p<0.001		* p<0.001		* p<0.001	

Clock Drawning, and both the Trial Making A and Trial Making B test) in order to check different domains of cognition.
Statistics: parametric and non parametric tests; anova and Duncan test, linear regression, assuming $p<0.05$ as the lower limit of significance. Results: a substantial deterioration of cognition was assessed in AS; CNOB, and COPD subjects, even if to an increasing extent and prevalence (anova $p<0.001$), but independently of gender.
The prevalence of cognitive dysfunction proved related to the psychometric tools used, Trial Making A and B test resulting the most sensitive ones. MRC and CAT scores, together with FEV1 % pred., PaO_2, and $PaCO_2$ were the variables most significantly related to the extent and the prevalence of cognitive deterioration. AS, CNOB, and COPD individuals aged 40-69 showed the highest difference from normal limits of cognition ($p<0.01$), thus suggesting that the chronically persistent airway insult might act as independent risk factor for worse cognitive function over these ages. It was particularly clear in COPD, where the extent of the cognitive deterioration assessed in subjects aged 40-69 was equiva-

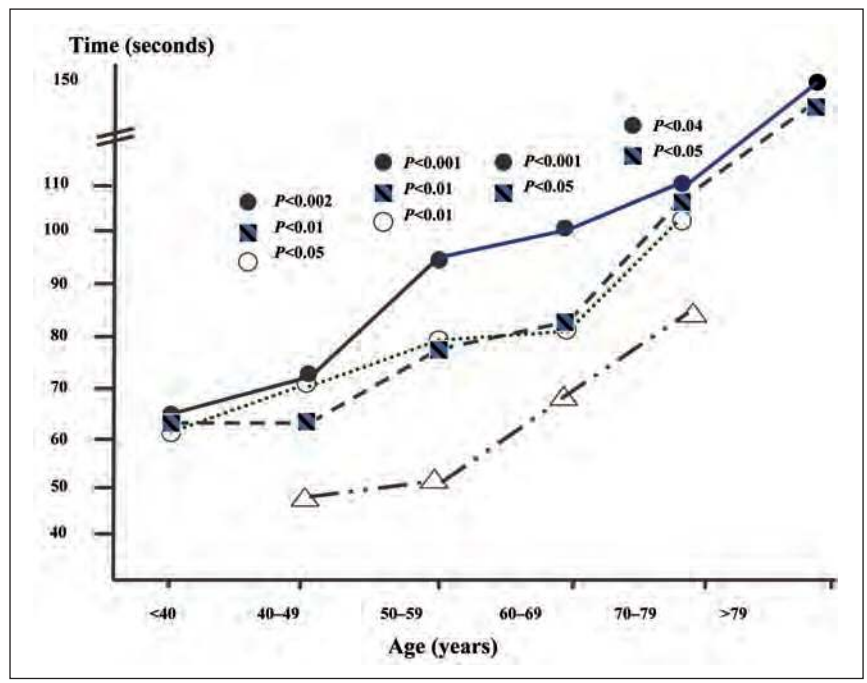

Figure 2 - TMT A test: comparison among the trends of cognitive impairment measured by decades of age (ANOVA) in AS (○), CNOB (▩), and COPD subjects (●) versus the corresponding normal reference values (△).

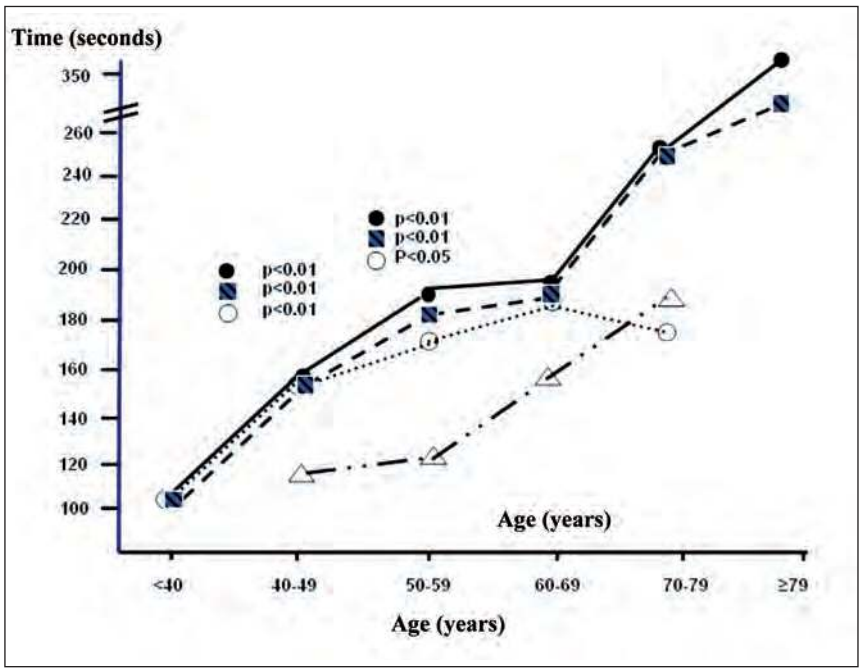

Figure 3 - TMT A test: comparison among the trends of cognitive impairment measured by decades of age (ANOVA) in AS (○), CNOB (▨), and COPD subjects (●) versus the corresponding normal reference values (△).

lent to that in normal individual aged >79years, thus confirming the strong ageing effect (an average of twenty years) of COPD.

Conclusions: cognition deteriorates maximally in severe COPD, but the occurrence of a significant impairment may start since the early stages of chronic airway damage. The cognitive dysfunction which characterizes subjects suffering from chronic airway disorders affects several domains of cognition, and may contribute to explain their insufficient adherence to therapeutic plans and strategies, and their increasing social costs. The assessment of cognition should be encouraged for completing the routine diagnostic procedures in this kind of subjects. Other studies oriented to focusing the psychometric profile of subjects with airway obstruction of different severity are welcomed, particularly if carried out by multiple lung function measurements and psychometric scores.

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***Roberto W. Dal Negro**, MD, FCCP Born in Verona (Italy), on May 17th,1947. In 1971 he graduated in Medicine (Modena University) and in 1974 obtained the Diploma of Specialist in Respiratory Diseases (Pavia University). After a period of research stages at the Academic Hospital of Utrecht, Lovain and Miami, in 1992 he became Head of the Lung Division at the Bussolengo Gen.Hosp.and in 2004 Head of the Dept. of Internal Medicine in Verona- Italy; At present he is Scientific Head of Centro Nazionale Studi di Farmacologia e Farmacoepidemiologia Respiratoria – Verona – Italy. He is Author of more than 700 scientific papers (in Italian, English, French, German) and of 28 monographs/books/chapters of books.*

Maurizio Vignola Award for Innovation in Pneumology
ERS Congress (Munich 9 Sept. 2014)

The ERS is pleased to present the Maurizio Vignola Award for Innovation in Pneumology, which is supported by the Chiesi Foundation and is dedicated to the memory of Professor A. Maurizio Vignola (1964-2004) in recognition of is outstanding contributions to the field of respiratory medicine.
The award is for the best publication within the scope of respiratory medicine and, more specifically, the basic mechanisms that underpin respiratory diseases. In 2014, the prize will be shared by the following two winners. They will respectively receive half of the total amount of E 18,000, which will be used to investigate the subject of their winning publications further.

The 2014 awardees are:


Dr. Kristin Westphalen

Dr. Kristin Westphalen (Munich, Germany) who published a paper in *Nature* entitled *"Sessile alveolar macrophages communicate with alveolar epithelium to modulate immunity"*.

During medical school, Kristin Westphalen started working at the University of Kiel. She wrote her medical thesis on the antiapoptotic signalling in cancer cells that is evoked by death receptor-mediated pro-apoptotic stimuli. After graduating from medical school in 2007, she began a residency in the Department of Anaesthesiology at the University Medical Centre Hamburg-Eppendorf. In 2010, she commenced a 3 year fellowship in lung research in Professor Jahar Bhattacharya's lab at Columbia University, New York. Her project addressed fundamental mechanisms of the acute lung injury that results when pulmonary alveoli are exposed to aspirated acid and inhaled indotoxin. The fellowship provided training in fluorescence imaging of the liver lung, lung micropuncture, and diverse cell and molecular approaches, including DNA and RNA methods, immunoblotting, flow cytometry, and mouse breeding. During her fellowship. During her hellowship, Dr. Westphalen made the paradigm-shifting discovery that alveolar macrophages communicate with the lung epithelium to suppress innate immunity. These findings were publisched in *Nature* in the paper that is awarded the 2014 ERS Maurizio Vignola Award. Since January 2014, she has been working as a clinical fellow in the Department of Anaesthesiology at Ludwig Maximilian University of Munich. She has also been selected as a principal investigator for the German Centre of Lun Research in association with the Comprehensive Pneumology Centre at the Helmoholtz Centre Munich.

Dr. Klaus Bonnelykke

Dr Klaus Bonnelykke (Copenhagen, Denmark), who published a paper in *Nature* Genetics entitled "*A genome-wide association study identifies CDHR3 as a susciptibility locus for early childhood asthma with severe exacerbations*".

Klaus Bonnelykke is and MD with training in paaediatrics. His research is based in the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) research centre, which is where he did his PhD and has worked for several years as a senior researcher. His research area can be described as clinical-translational research that combines the clinical data from birth cohort studies with basic research methodologies. The focus of this research is on the early origins childhood asthma, allergy and eczema, with a special emphasis on genetics. This research has led to intersting results that caused Klaus to focus more specifically on the genetic background of childhood asthma with severe exacerbations by performing the first genome-wide association study (GWAS) on this asthma phenotype. The results were published in the paper that is awarded the 2014 ERS Maurizio Vignola Award.

From left: Marisa Bonsignore, Kristin Westphalen and Maria Paola Chiesi

From left: Marisa Bonsignore, Klaus Bonnelykke and Maria Paola Chiesi

Identification of novel compounds by 3D-QSAR and from natural world able to reduce the expression of proinflammatory interleukin-8

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Adriana Chilin[2],
Alessandra Guerrini[1],
Gianni Sacchetti[1], Ferruccio Poli[3],
Ilaria Lampronti[1],
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NF-κB is a transcription factor involved in the control of a large number of normal cellular and organism processes, such as immune and inflammatory responses, cellular growth and apoptosis (1-3). One of the most important NF-κB regulated targets is the gene coding the proinflammatory cytokine IL-8 (4). In this way, targeting NF-κB and IL-8 could be of great interest in order to find new therapeutic agents, mainly anti-inflammatory compounds (5).

In order to identify compounds able to inhibit NF-kB and modulate the IL-8 expression we have investigated: (a) new psoralen derivatives analyzed by threedimensional quantitative structure-activity relationship (3D-QSAR) analysis; (b) polyphenols rich extracts derived from waste water from olive mill, by a molecular imprinting approach; (c) eleven decoctions, from indian plants widely used in ayurvedic medicine.

Initially, electrophoretic mobility shift assays (EMSAs) were performed to determine whether the different active principles were able to inhibit the binding between transcription factor (TF) NF-κB and DNA consensus sequences. Moreover we investigated IL-8 gene expression by Real-Time and Bioplex (BIO-RAD) technology in IB3-1 cystic fibrosis (CF) cell line, isolated from human bronchial epithelium and stimulated by pro-inflammatory stimulus TNF-α.

In Marzaro G. et al., 2013 (6), starting from molecular docking studies, several possible protein binding sites were proposed and 3D-QSAR models were built using the docked poses of 29 (the most active psoralen in the series) as templates for alignment of the inhibitors. All the collected data allowed the identification of compound 29 as a potential candidate for the development of anti-inflammatory strategy since they exhibited high efficiency in inhibiting NF-κB/ DNA interactions and also IL-8 gene expression in TNF-α treated IB3-1 CF cells (Figure 1A).

In Lampronti I. et al., 2013 (7), we have demonstrated apigenin and

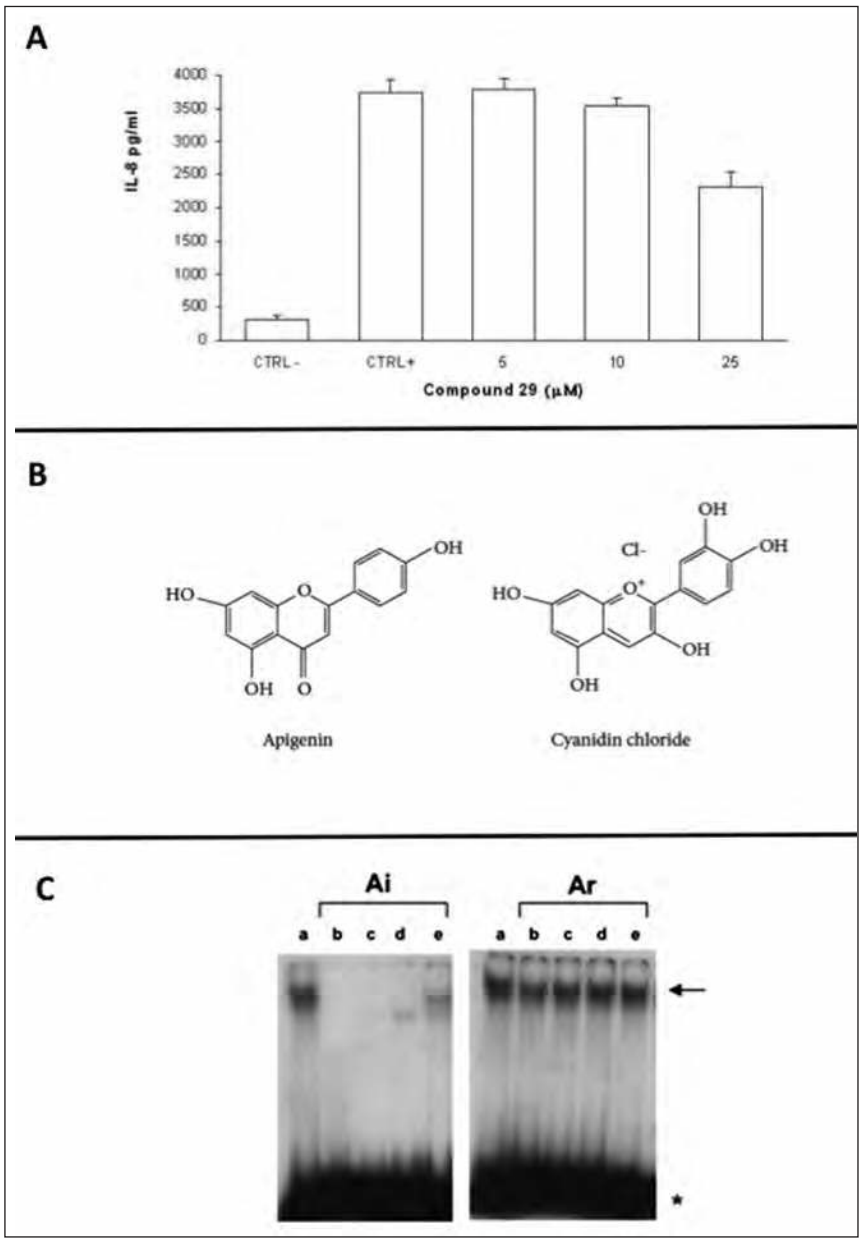

Figure 1 - (A) Effects of compound 29 on TNF-α induced IL-8 gene expression in IB3-1 cells by Bioplex analysis of IL-8 protein present in supernatants; (CTRL –) untreated IB3-1 cells; (CTRL +) TNF-α treated IB3-1 cells. For each experiment duplicate RT-PCR determinations were performed. Results represent the average ± SD of three independent experiments. Modified from Figure 10, Marzaro G. et al., 2013 (6). (B) Chemical structures of the most active principles identified in olive oil extract. Modified from Figure 2, Lampronti I. et al., 2013 (7). (C) Representative EMSA assays for two decoctions (Ai: *Azadirachta indica*; Ar: *Asparagus racemosus*) with different ability to inhibit NF-κB p50/DNA interaction. Ten ng of human NF-kB p50 protein and different concentrations (a: 0; b: 5 μg/μl; c: 1.25 μg/μl; d: 0.3 μg/μl; e: 0.075 μg/μl) of decoctions were pre-incubated for 20 min at room temperature, then 0.25 ng of 32P-labeled DNA/DNA target molecules was added to the samples for further 20 min at room temperature. Protein/DNA complexes were separated by polyacrylamide gel electrophoresis, and autoradiography was performed. The arrow indicates protein/DNA complexes. *indicates the free ^{32}P-labeled NF-kB oligonucleotides. Modified from Figure 1, Guerrini A. et al., 2014 (8).

cyanidin chloride (Figure 1B), obtained from polyphenols rich extracts derived from waste water, were able to modulate the expression of the NF-kappaB-regulated IL-8 gene.

Finally in Guerrini A.G. et al., 2014 (8), eleven decoctions, obtained from indian plants widely used in ayurvedic medicine, were investigated and seven decoctions (*Azadirachta indica*, *Terminalia*

bellerica, *Terminalia chebula*, *Hemidesmus indicus*, *Emblica officinalis and Swertia chirata*) were the most active in inhibiting NF-kB/DNA interactions by EMSA assay (Figure 1C) and in reducing proinflammatory IL- 8 expression in our cellular model.

Conclusions

NF-κB is one of the master transcription factors responsible for inflammation in many diseases such as rheumatoid, arthritis, cystic fibrosis, chronic obstructive pulmonary disease (COPD). Accordingly, compounds that bind to NF-κB, thus interfering with the NF-κB/DNA interaction and inhibiting IL-8 expression are of great importance and can be identified from natural products or by computational approch as reported in our results.

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Monica Borgatti *received the degree in Chemical and Pharmaceutical Technologies from Ferrara University in 1999 (magna cum laude). She obtained the Ph.D. in Biotechnology at the Department of Biochemistry and Molecular Biology, Ferrara University in 2004. She worked as Post doctoral fellow, in the Department of Biochemistry and Molecular Biology, University of Ferrara (20042011). Since 01/11/2011 she has been working as researcher at Department of Biochemistry and Molecular Biology, Pharmacy Faculty, Ferrara University. In the June 2003 Monica Borgatti received CIB Young Researcher prize. Her research interests are on various aspects of molecular biology, gene therapy, and pharmacogenomics in particular: peptide nucleic acids as molecular strategy to modify gene expression in the treatment of cystic fibrosis and HIV-1 infections and as molecular probes for innovative diagnosis tools; analysis of novel molecules with potential anti-inflammatory activity; biological evaluation of novel compounds as inducers of erythroid differentiation for possible use in the therapy of haematological diseases as beta-thalassemia; biological and diagnostic applications of dielectrophoresis (DEP) based Lab-on-a-chip devices to drug research and development. More than 90 papers, published by Monica Borgatti, are available in Medline and she is co-inventors for five patents.*

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Chance and its Rules

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The return of summer, like every year, generates the talk of heat in newspapers, on television, and at home as if it were an exceptional event. Why is it that every year people seem to say that it is hotter than the last? Perhaps it is true, but usually the scientific data to support that affirmation is lacking and it seems to be just a cliché. The assertion falls into the same category as the motherly incitation to generations of reluctant children to eat their spinach, erroneously believed to be high in iron. What is the way out of what is defined as "the disease of hasty generalisation"?

The answer is in the application of statistical methods, whereby in an exact and objective fashion we rely on rational procedures and apply them unconsciously and approximatively, while in daily practice we use our "common sense". In other words we attempt to find a scientific basis for our personal judgement, thereby reducing the risk of subjectivity and approximation and, as follows, error.

In general, statistical method is applied in two main circumstances: *a)* when analysing complex situations, to describe its characteristics without drawing any particular conclusions- in this case we are talking about *descriptive statistics*, which was historically the first application of statistics: *b)* when starting with a limited number of cases known as *the sample* the search is expanded to find information on the properties and characteristics of a large number of subjects, *the population or statistical universe*. In this case we are talking about *inferential statistics*.

When statistical method is applied to medical science and biology in general, the existence of biological variability, an intrinsic and indelible property of human beings, must be taken into consideration. In nature, the causes which make an observation unique are infinite and unpredictable. The totality of the multiple unknown and difficultly appreciated factors influencing and determining a phenomenon beyond our control and predictions, is described as *chance*. Chance, therefore, is the fortuitous, accidental, unpredictable, and irrational event occurring independently of our will and regardless of any law of causality. From a purely speculative point of view, the importance of chance as a

promoter of changes in nature and the world was noted in the cosmology of Empedocles of Agrigentum (440 a.C.), who was also the founder of a medical school. With the Epicureans, chance, after having eliminated any role of cosmic intervention, becomes for the first time in the history of philosophy the basis for man's metaphysical liberty. Whether in Aristotle's or Epicurus' casualism, chance negatively influences experiments by way of biological variability, the difference between individuals. Statistical methods attempt, without ever completely cancelling, to contrast these interferences. On the other hand, paradoxically, chance becomes *condicio sine qua non* of statistical reasoning. In fact, every assumption in statistics can only be correctly interpreted by the theory of probability, which is none other than the mathematical application to biological events of empirical laws to which chance obeys.

Experimental psychology, developed over the last century, is credited with having transformed the calculation of probabilities from mathematical amusement into a precious instrument for experimental research. Historically, the fundamental call for a scientific protocol in research is credited to "On the Origin of Species", published in 1859, in which Darwin revoked from man the title of "king of creation" by considering him rather as the result of natural evolution. While Darwin was influential in advancing experimental method, the father of modern statistics was Ronald A. Fisher. He was a student in the early '900 of Karl Pearson, professor of applied mathematics at the University College of London. Fischer was the first to understand the importance of experimental design, establishing the golden rule still used by researchers today: *experiments, in any field whatsoever, must be planned prior to being undertaken.* Prior to gathering any data, it is of fundamental importance to identify the scope of the study by preparing what Fisher called the *factorial design* , by which it is possible to predict the role and reciprocal interactions of all the factors in play. The biggest and most revolutionary innovation however, was the discovery that every experimental design, no matter how accurate and sophisticated, can only demonstrate if the *null hypothesis* or *zero hypothesis* (*H*0) can be accepted or refuted. If it is accepted, it is demonstrated that the factors in play are not different from one another and come from the same population; eventual differences between them are attributed to chance and therefore non-significant. If on the other hand the null hypothesis is refuted, it is demonstrated that the factors being examined do not originate from the same population and are therefore significantly different. Therefore the alternative hypothesis (*H*1) can never be demonstrated, not even by numerous studies, but will only have a major probability of being

upheld. The level of probability within which the statistical method deems acceptable a hypothesis is 5%. This premise represented not only the starting point of one of the biggest revolutions in statistical methodology but also served as a shield against the doctrines in vogue at the time, dogmatic truths which could constitute an ideological base endangering experimental hypothesis.

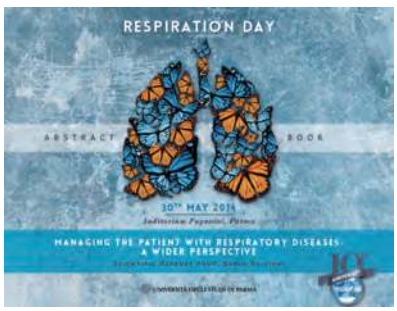
Again at Pearson's statistics school began the first studies on *sampling*, which is the fundamental moment in preparing a study and is again subjected to the effects of chance. While W.S. Gosset, who became famous under the pseudonym Student, was the first to work on samples smaller than those previously used in common scientific studies, Fisher was the first to understand the importance of casual or random sampling. Up until that point, researchers picked and chose samples in a whimsical and extravagant fashion. For example, Pierre-Simon de Laplace, the greatest French mathematician of the Napoleonic epoch, chose the towns he used for demographic studies based on the entrepreneurship of their mayors.

In order to avoid systematic errors, the sample must have the following characteristics: a) be sufficiently numerous, since the validity of the estimate increase s as does the sample size; b) must be rigorously *casual* , in such a way that each individual of the original population has an equal probability of being included; c) to be *homogeneous*, meaning to originate from a population in which each unit is as similar as possible to the other.

Only if the sample corresponds to these three prerequisites will it really be representative of the original population. Nevertheless, there will always be differences in the values observed in the sample and the original population. If the choice of the sample subjects was made according to rigorous casual criteria, then it is possible to calculate a *confidence interval* within which there is a good probability the unknown value will fall. *Randomisation* is therefore the only system which allows to predict the entity of error due to chance. In other words, it can be said that statistics is in itself paradoxical in that it fights against the negative effects of chance on experiments by using the very laws to which chance obeys.

Once the problem of sampling is overcome, the next step in the statistical process is to use tests of significance, not to demonstrate the experimental hypothesis but rather to verify the null hypothesis. As Popper maintained, the way to distinguish between scientific and non-scientific reasoning is the possibility of confutation, by subjecting the hypothesis to numerous attempts to dispute its validity. Statistical tests and the modality in which to apply them will be addressed in the next update.

eRn



Ten Years of Respiration Day in Parma (2004-2014)

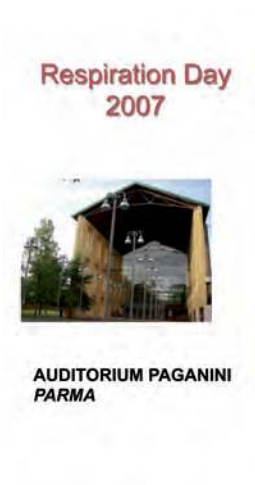
Respiration Day was born 10 years ago with the aim to annually convene Specialists from all over the world and openly discuss about hot topics which can have an impact on daily clinical management of patients with respiratory diseases. This decade has been particularly exciting for the scientific advance in understanding the pathophysiology of these diseases, which are becoming more and more relevant in social terms. At the same time, technological equipment and therapeutic options have strongly improved, thus allowing a better diagnosis and a more effective treatment. However, a lot can still be done to obtain an even more successful management. Having this challenging objective in mind, the 10th anniversary edition of "Respiration Day" aims at highlighting and dissecting different aspects of respiratory disease physiopathology and management, and of their social impact.

Colorno" 2005

Following one year of preparation, the 1st Respiration Day took place in 2005 in ***Colorno***, near Parma, in the wonderful setting of the Royal Palace of Maria Luisa. The event was jointly organized by the University of Parma and the Chiesi Foundation and was **dedicate**d to: "*The evolving challenge of Chronic Respiratory Diseases*" About 100 people attended this first meeting. The former *Rector* of the University (Prof. *Gino Ferretti*) took part in the Opening Ceremony. Also *Alberto Chiesi*, The President of Chiesi Farmaceutici attended the meeting and *Paolo Chiesi*, the President of the Chiesi Foundation, was among the speakers.

Star Hotel 2006

In 2006 Respiration Day took place at an elegant Hotel in Parma, since the Royal Palace in Colorno was insufficient to accommodate the increasing number of participants.
The main topic was: *Asthma and COPD* and their most important *biological and clinical aspects.*



Auditorium Paganini 2007

In 2007, for the first time, the event took place at the Auditorium Paganini, the only place in Parma that could accommodate some hundred people.
The Auditorium is an old sugar mill, renovated by the Architect Renzo Piano and readapted to be used as a musical and scientific venue.
The topic of the meeting was: *New guideline for Asthma and COPD*

Auditorium Paganini 2008

In 2008, the main topic to be discussed was:
Co-morbidities in Asthma and COPD
Moreover, for the first time, unusual *clinical cases* were presented and discussed with the participants

Auditorium Paganini 2009

The 2009 edition of the meeting was dedicated to : *Similarities and differences between Asthma and COPD* and *to Management of patients with chronic inflammatory airway disease*

Auditorium Paganini 2010

In 2010, the main topic was: *From Randomized Clinical Trials to Clinical Practice* and the new format of *"Exchange of clinical experiences between clinicians of different nationalities"*

Auditorium Paganini 2011

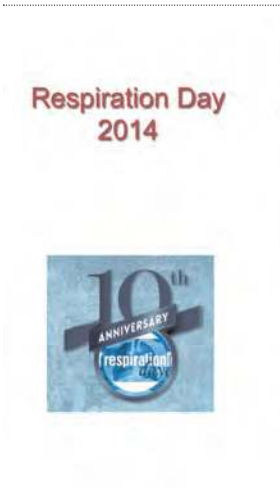
In 2011 the attention was devoted to:
- Research and clinical themes
- Moreover, a clinical ground round (with the presentation of 3 cases) was organized and the format was highly appreciated by participants

Auditorium Paganini 2012

The main topic of the 2012 RD was highly innovative, since it was:
- *Personalized Medicine*
- and the possibility of *targeted therapy*

Auditorium Paganini 2013

Last year *Exacerbations in Asthma and COPD were discussed*
In particular, were analysed:
a) Exacerbations *Induced by infections*
b) *Non-infectious* exacerbations



Auditorium Paganini 2014

This year the program is devoted to:
a) IPF as a model of inflammatory disease
b) Than: Asthma and COPD overlap syndrome
c) COPD: from new guidelines to practice
d) Presentation of clinical cases (IPF, COPD, severe Asthma)

Speakers

In every meeting speakers came from all over the world: in 10 years more than 100 scientist and clinicians from many Countries attended the Respiration Day in Parma, presenting new topics and discussing original data.

Respiration Day: Speakers 2005-2014

Country	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	N.
I	5	3	3	4	2	3	6	4	4	5	39
B					1	1			1		3
D			1	1		1	2		2	1	8
DK							1			1	2
E		1	1		1	1	1	1			6
F		1	1		1	1					4
GR					1	1					2
NED	1	1	1	1	1	2		1			8
UK	1	2		1	2	4		3	1	2	16
Sw			1								1
Brazil							1				1
Canada		1	1	2	1	1	2	1	1	1	11
Russia			1								1
USA			2		2	1		1		1	7
Total	7	8	12	10	11	16	14	11	9	11	109

Participants

The number of participants *regularly increased* year by year, such as the *number of Countries* invited.

Respiration Day 2014: Participants

Italy	117	Middle-East	21	Slovakia	3
Turkey	25	Poland	74	Maghreb	38
Netherlands	22	Uk	18	Brazil	44
Bulgaria	20	France	13	Mexico	11
Cee (Belarus+Balkan-Baltics)	45	Czech Republic	32	China	13
Spain	52	Romania	5	Russia	13
Hungary	17	Slovenia	38		
Germany	47	Austria	13		
Nordics	20	Belgium	30	**Partecipants: 731**	

Remembering Maurizo Vignola

Today Maurizio would be fifty year old, maybe his hair would be gray, and he would talk about his children with pride and some anxiety about their future. Perhaps he would feel a heavy load of responsibilities and the difficulties of our times. Certainly he would still be one of the best pulmonologists in the world. Time went by quickly, but Maurizio is still part of our daily life. Many times we have recalled episodes shared with him at work, on travel, or during sunny days at the beach. In these years, we saw his children grow, and were emotionally struck at seeing him again in his son Andrea who looks very much like him. The acute pain caused by his death decreased over time, but the regret for the loss of a friend did not subside. After so many years, reading his clear and innovative papers confirms his high scientific maturity. His enthusiasm was contagious, and my father used to say: "while you all are on the earth, Maurizio flies!", charmed by his energy and the relentless pace of his work. Maurizio' s life was short but complete, he left a durable sign in the scientific community and in the people who had the privilege to work with him. After the highly emotional wave linked to the onset of his disease, his courageous fight against it in the hope of recovery, and his premature death, we are left with the memory of a man of great value, which will continue to live and be an example for all of us.

Marisa Bonsignore

Curriculum vitae

1964 Born in Palermo

1989 Medical Doctor, Full Marks and Honors at the University of Palermo

1993 Board Pulmonary Medicine, Full Marks and Honors at the University of Palermo

1993-3 Research Fellow at the University of Montpellier (Pr. J. Bousquet)

1992 Visiting Scientist at the University of Nebraska (Prof. S. Rennard)

1998 European PhD in Respiratory Pathophysiology at the University of Montpellier

2004 Died in Genova

Academic appointments

1993 Junior Scientist, National Research Council

1998 Senior Scientist, National Research Council

1999 Associate Professor of Respiratory Medicine, University of Palermo

2000-4 Full Professor of Respiratory Medicine, University of Palermo

Editorial boards

1999 European Respiratory Journal

1999 Respiratory Researce, Associate Editor

2000 Current Opinions Allergy&Immunology

2000 European Respiratory Journal, Chief Section Editor

2003 Allergy

Publications

> 120 original papers in peer reviewed journals

> 30 review/book chapters

Research fields

- Lung physiology and pharmacology
- Mechanisms of airway inflammation in rhinitis and asthma
- Mechanisms of lung inflammation in COPD
- Pharmacology and pharmacogenetics of asthma and COPD
- Genetics of asthma and COPD