



## Maurizio Cutolo

Full professor

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### *Education and training*

1978

#### **Degree in Medicine Surgery**

Pathophysiology of Vasculitis - 110/110 magna cum laude  
University of Naples - Naples - IT

1982

#### **Postgraduate on Rheumatology**

Rheumatoid arthritis - 50/50 magna cum laude  
University of Genova - Genova - IT

1987

#### **Postgraduate on Internal Medicine**

Trace elements in rheumatic diseases - 50/50 magna cum laude  
University of Genova - Genova - IT

### *Academic experience*

1998 - 2000

#### **Associate Professor on Internal Medicine**

University of Genova - Genova - IT  
Chief Research and inpatient out patients t clinics

2006 - ONGOING

#### **Director Postgraduate School of Rheumatology**

University of Genova - Genova - IT

### *Work experience*

2000 - ONGOING

#### **Full Professor of Rheumatology**

University of Genova - Genova - IT  
Director Research Laboratories - Divisions of Rheumatology - Postgraduate  
School on Rheumatology

### *Language skills*

#### **English**

Proficient

FELLOWSHIP at the  
New York  
University NEW  
YORK USA 1983  
1986

## ***Teaching activity***

Prof. Cutolo teach to undergraduate students, Postgraduate fellows and PhD Students.

## ***Postgraduate research and teaching activity***

### **Supervision of PhD students, residents and post-doctoral fellows**

- Prof. Cutolo is Director of the Postgraduate School on Rheumatology
- The total number of fellows every year is of 12 (4 years with 3 fellows each year). The School has been accredited since 1976 and the Ministerial Site Visit in 2016 confirmed the high level of the School.
- The School of Rheumatology is also official teaching center for Postgraduate PhD students on Clinical Immunology and several PhD have been graduated in the last years. The education is done at the Research Laboratories and at the Clinical inpatients and outpatient Divisions.
- Several bursaries for Biologists, Students and MDs are offered every year. Biologists working at present in the LABs are under the supervision of Prof. Cutolo.

## ***Research interests***

### **Neuroendocrine Immunology of Rheumatic Diseases**

Central (CNS) and peripheral nervous systems integrate and coordinate the functions of all structures of the living organism and among those, also of immune system. Recent evidences have shown that, at the same time, immune system cells and products have an afferent arm through which they communicate to CNS, with effects on behaviour, thermoregulation and sleep (sleep is an adjuvant of the immune system activation). Circadian rhythms drive the daily immune system activation through hormones such as melatonin and cortisol, and in particular activate the immune response during the night in case of chronic inflammatory diseases such as rheumatoid arthritis. To this purpose, for instance, the study of a possible presence of adrenocortical insufficiency (related to the chronic stress induced by the diseases) through baseline dynamic testing of adrenal function, adrenal glucocorticoids and steroids evaluation, should be performed, together with monitoring of morning inflammatory biomarkers and joint symptoms.

### **Vitamin D, steroid hormones, and autoimmunity.**

The endogenous serum metabolite of vitamin D (calcitriol, 1,25(OH)<sub>2</sub> D<sub>3</sub>) is

considered a true steroid hormone (D hormone), and like glucocorticoids (GCs) and gonadal hormones, may exert several immunomodulatory activities. Serum vitamin D deficiency (25(OH) D), and therefore reduced 1,25(OH)<sub>2</sub> D<sub>3</sub> availability, is considered a risk factor for several chronic/inflammatory or autoimmune conditions, including infectious diseases, type 1 diabetes, multiple sclerosis, and especially autoimmune rheumatic diseases (ARD). In ARD in particular, 1,25(OH)<sub>2</sub> D<sub>3</sub> regulates both innate and adaptive immunity, potentiating the innate response (antimicrobial activity) but reducing adaptive immunity (antigen presentation, T and B cell activities). Regarding a possible synergism between vitamin D and GCs, several studies show that 1,25(OH)<sub>2</sub> D<sub>3</sub> has significant additive effects on dexamethasone-mediated inhibition of human lymphocyte and monocyte proliferation. Conversely, vitamin D deficiency seems to play a role in increasing autoantibody production by B cells, and seasonal vitamin D declines may trigger flares in ARD, as recently shown. Finally, 1,25(OH)<sub>2</sub> D<sub>3</sub> seems to reduce aromatase activity and limit the negative effects related to increased peripheral estrogen metabolism (cell proliferation, B cell overactivity).

#### **Glucocorticoids and chronotherapy in rheumatoid arthritis.**

It is evident that the morning symptoms of rheumatoid arthritis (RA) are linked to the circadian abnormal increase in night inflammation, favoured by inadequate cortisol secretion under conditions of active disease. Therefore, exogenous glucocorticoid treatment is recommended in RA at low doses since it may partially act like a 'replacement therapy'. The prevention/treatment of the night upregulation of the immune/inflammatory reaction (and related flare of cytokine synthesis) has been shown to be more effective when exogenous glucocorticoid administration is obtained with a night-time-release formulation. Large-scale trials documented that modified-release prednisone has greater efficacy than morning prednisone for long-term low-dose glucocorticoid treatment in patients with RA, showing at least a more significant reduction in morning joint stiffness. Interestingly, despite a considerably higher cost than conventional prednisone, chronotherapy with night-time-release prednisone was recognised as a cost-effective option for patients with RA not on glucocorticoids who are eligible for therapy with biological disease-modifying antirheumatic drugs (DMARDs). Moreover, since different cell populations involved in the inflammatory process are particularly activated during the night, other therapeutical approaches used in RA, for example, conventional DMARDs and non-steroidal anti-inflammatory drugs (NSAIDs), should follow the same concepts of glucocorticoid chronotherapy. Indeed, bedtime methotrexate chronotherapy was found to improve RA symptoms compared to the current standard dosing methods, and several available NSAIDs (ie, indomethacin, aceclofenac, ketoprofen, flurbiprofen, lornoxicam) have been very recently modified in their formulation, in order to obtain chronotherapeutical effects in RA.

#### **Capillaroscopy in systemic sclerosis**

Capillaroscopy is a non-invasive and safe tool to morphologically study the microcirculation. In rheumatology it has a dual use. First, it has a role in differential diagnosis of patients with RP. Second, it may have a role in the

prediction of clinical complications in CTDs. In SSc, pilot studies have shown predictive associations with peripheral vascular and lung involvement hinting at a role of capillaroscopy as putative biomarker. Also and logically, in SSc, microangiopathy, as assessed by capillaroscopy, has been associated with markers of the disease such as angiogenic/static factors and SSc-specific antibodies. Moreover, morphological assessments of the microcirculation (capillaroscopy) seem to correlate with functional assessments (such as laser Doppler). Because of its clinical and research role, eyes are geared in Europe to expand the knowledge of this tool. Both the European League Against Rheumatism (EULAR) and the ACR are stepping forward to this need.

- Cutolo M, Sulli A. Testing anti-osteoclastic function of DMARDs in RA. *Nat Rev Rheumatol*. (in press) 2018
- Burmester GR, Bijlsma JWJ, Cutolo M, McInnes IB. Managing rheumatic and musculoskeletal diseases - past, present and future. *Nat Rev Rheumatol*. 2017 Jul;13(7):443-448.
- Cutolo M, Sulli A. Therapy. Optimized treatment algorithms for digital vasculopathy in SSc. *Nat Rev Rheumatol*. 2015 Oct;11(10):569-71.
- Cutolo M. Rheumatoid arthritis: circadian and circannual rhythms in RA. *Nat Rev Rheumatol*. 2011 Aug 2;7(9):500-2.
- Cutolo M, Sulli A, Smith V. Assessing microvascular changes in systemic sclerosis diagnosis and management. *Nat Rev Rheumatol*. 2010

## Grants

2014 - ONGOING

### GLORIA The Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis Study

European Commission Horizon 2020 - IT Participant

**Rationale:** Rheumatoid arthritis (RA) is a condition with high impact both on the individual and society. In the context of comparing the effectiveness of existing healthcare interventions in the elderly, RA is a condition highly relevant to the community since it has a strongly negative impact on the quality of life of the individual, is particularly frequent in the elderly, and is associated with significant costs. RA management remains challenging: there is an urgent unmet medical and societal need for improved treatment strategies that are effective, safe and affordable.

**Objective:** The primary objectives of the GLORIA project are twofold: a) To assess the effectiveness, safety and cost-effectiveness of low-dose GC therapy (5 mg/day) compared to placebo given for two years as co-treatment for elderly RA patients ( $\geq 65$  years) in a pragmatic randomized trial; b) To assess study medication adherence through a medication packaging solution, and test the effectiveness of smart device technology to improve adherence. Other objectives of the GLORIA project are: to deliver an outcome prediction model for individual patient outcome.

**Study design:** The GLORIA study is a randomized, double-blind, placebo-controlled pragmatic multicenter clinical trial to assess the effectiveness and safety of a daily dose of 5 mg prednisolone or matching placebo in elderly RA patients. Patients will be randomized into two arms: the experimental arm (receiving prednisolone 5 mg/day) or the control arm (receiving placebo). Our design emulates the routine care setting: eligibility criteria are very liberal, assessments and procedures are tailored to represent standard of care, and concurrent antirheumatic treatment is allowed next to the trial medication with minimal limitations. Furthermore, all patients will have an adherence monitoring device loaded into the cap of the drug bottle; adherence data will be monitored throughout the trial. In addition, to test the effect of adherence reminders, a substudy (another trial) will be nested in the main GLORIA trial.

**Study population:** Patients of 65 years of age and older with RA according to the 2010 classification criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), requiring antirheumatic therapy because of inadequate disease control, as evidenced by a disease activity score of 28 joints calculated with *erythrocyte sedimentation rate* (DAS28)  $\geq 3.20$ .

## ***Editorial activity***

### **Editorial Work**

- 2007-member Advisory Editor of Arthritis & Rheumatism
- Member of the board of: Annals of the Rheumatic Diseases (since 1999), Rheumatology (1998-2008), Current Opinion Rheumatology, Autoimmunity Review, Journal of Autoimmunity. Revista Portuguesa de Reumatologia, Reumatismo
- 1991-present Associate Editor of Clinical and Exp Rheumatology

### **Selection of Books and chapters in books**

- Editor of the volumes of the Annals of the New York Academy of Sciences: “Neuroendocrine Immune Basis of the Rheumatic Diseases” (vol 876/1999, vol 966/2002, vol 1069/200 and vol 1193/2010)
- CoEditor of the volumes of the Annals of the Rheumatic Diseases Clinics of North America “Neuroendocrine Immunology of the Rheumatic Diseases” (Saunders) (vol 26:4/ 2000, vol 31:1/2005)
- CoEditor of the volume 22, issue 6: “Modern imaging techniques: a revolution for rheumatology practice”. Best Pract Res Clin Rheumatol (Elsevier) - 2008
- Editor of the first textbook on capillaroscopy entitled: Atlas of capillaroscopy in Rheumatic Diseases - Elsevier 2010 under the aegis of EULAR
- Chapter “Neuroendocrine immunology in rheumatic diseases” in the EULAR Compendium on Rheumatic Diseases (2009, chapt 50 BMJ and chapter 2 in the 2013 edition)
- Chapter “Arthritis Accompanying Endocrine and Metabolic Disorders”

- in the Kelley's Textbook of Rheumatology (2010-2011, chap 121),
- Chapter "Effects of the Neuroendocrine System on Development and Function of the Immune System" in Rheumatology - Fifth edition by Marc C. Hochberg, Alan J. Silman, Josef S. Smolen, Michael E. Weinblatt, MD, and Michael H. Weisman, MD. (2010, chap 24, Elsevier).
- - Varga J, ed. Scleroderma: From pathogenesis to Comprehensive Management. New York: Springer Science+Business Media, LLC. 2012. Chapter: Cutolo M, Smith V. Nailfold Capillaroscopy, p 331-346.
- - 1st EULAR On-line Course on Systemic Sclerosis September 2011 - June 2012.

Module: 3. Cutolo M, Smith V. Assessment tools of the microcirculation.

- - Cutolo M & Smith V, eds. Novel insights into systemic sclerosis management. Future Science Group. 2013.
- - 3rd EULAR On-line Course in Systemic Sclerosis September 2013 – June 2013. Module: 3. Cutolo M, Smith V. Nailfold capillaroscopy and other methods to assess the microvasculopathy in systemic sclerosis.
- - Hachulla E & Czirjak L, eds. EULAR Textbook on Systemic Sclerosis. BMJ. 2013. Chapter: 14. Cutolo M, Smith V. Nailfold capillaroscopy and other methods to assess the microvasculopathy in systemic sclerosis, p 129-138.
- - Wigley F et al, eds. Raynaud's Phenomenon – A guide to Pathogenesis and Treatment. Springer Publishing. 2014. Chapter: 10c. Cutolo M, Smith V. Nailfold capillaroscopy.

## *Assignments abroad*

### **International Activities**

- 2005-2008 Vice President of the International Society for Neuroimmunomodulation (ISNIM)
- 2008-present Member of the Executive Committee, International Society for Neuroimmunomodulation
- 2004-2007 Vice President of the Italian Society for Rheumatology
- 2003 at present Member of the Scientific Committee of EULAR
- 2009-2011 Chairman of the European Ligue Against Rheumatic Diseases (EULAR) Standing Committee for Education and Training (ESCET)
- 2013-2015 member of the EULAR Foundation for Research FOREUM
- 2011-2013 **President-elect of EULAR (member Steering Group)**
- **2011-2015 President EULAR**
- **2014-2015 President of ILAR**
- **2016-2017 Past President EULAR and member Steering Group**
- **2016-present Deputy Chairman** of the European Network of rare connective tissue diseases (ERN ReCONNET)
- **2017 – present** Chairman of the Classroom Board of the EULAR School of Rheumatology (ESoR)

### **Congress Organisation**

- Executive President, the EULAR Congress of Rheumatology in Rome 2010 and 2015
- Organizer and Chairman of the 5 International Conferences on Neuroendocrine Immune Basis of the Rheumatic Diseases (1998, 2001,2005, 2009,2013)
- Chairman of the Workshops on Capillaroscopy and Rheumatic Diseases during the annual EULAR Congresses (2003, 2004, 2005, 2006,2008, 2010, 2011, 2012, 2013, 2014,2015,2016,2017,2018)
- Organizer and Chairman of the EULAR Courses on Capillaroscopy and Rheumatic Diseases (2004, 2006, 2008, 2010, 2012, 2013, 2014, 2016, 2018)
- Chairman of the EULAR Postgraduate Courses (2009 and 2010)
- Board of Organizers of the International Conferences on Sex Hormones, Pregnancy and Rheumatic Diseases (2005,2007,2009,2011,2013)

### **Scientific Societies**

- 2006-present CoFounder and Board member of the Italian Foundation for Arthritis Research (FIRA)
- 1999-present Board member of the American Autoimmune Related Diseases Association (AARDA)
- 2001-present Founder and Chairman of the EULAR Study Group on Neuroendocrine Immunology of Rheumatic Diseases (NEIRD)
- Coordinator of the EULAR-ESCET task force on “Learning Tools” in Rheumatology (first produced DVD on the EULAR website)
- 2005-present member of the EULAR task force on “glucocorticoids”
- 2004-present member of the EULAR Scleroderma Trials And Research (EUSTAR) group from (convenor for the capillaroscopy)
- Tutor for the module 52 in the EULAR Course on line (from 2010).
- Founder (1999) and Past-Chairman of the Study Group on Neuroendocrine Immunology (NEI) at the American College of Rheumatology (ACR)
- Founder (2010) and coChairman of the Study Group on Capillaroscopy in Rheumatic Diseases at the American College of Rheumatology (ACR)

### **Editorial Work**

- 2007-member Advisory Editor of Arthritis & Rheumatism
- Member of the board of: Annals of the Rheumatic Diseases (since 1999), Rheumatology (1998-2008), Current Opinion Rheumatology, Autoimmunity Review, Journal of Autoimmunity. Revista Portuguesa de Reumatologia, Reumatismo
- 1991-present Associate Editor of Clinical and Exp Rheumatology

## **Memberships**

- Member of the FP7 EU Board of evaluators (Bruxelles)
- 1980-present member of the Italian Society for Rheumatology
- 1985-present member of the American College of Rheumatology
- 1986-present member of the British Society for Rheumatology
- 2010 Honorary Member of the Hungarian Association of Rheumatologists
- 2011 Honorary member of the Russian Society for Rheumatology
- 2014 Doctor Honoris Causae in Medicine University of Bucharest

## **Main fields of investigation**

- Neuroendocrine immunology in rheumatology,
- sex hormones, stress and circadian rhythms in rheumatic diseases,
- glucocorticoid management of rheumatoid arthritis,
  
- videocapillaroscopy in systemic sclerosis and other rheumatic diseases,
- Laser doppler analysis of the peripheral blood flow,
- new biological drugs for treatment of rheumatoid arthritis (LAB research and clinical phase I trials)
- Vitamin D endocrine system in Rheumatic diseases and cancer

## ***Other professional activities***

already described see before