**Brain Medicine** 

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## **INNOVATORS & IDEAS: RESEARCH LEADER**

## Genomic Press BRAIN MEDICINE From neurons to behavior and better health

Francesco Benedetti: Breaking boundaries between modern psychiatry and clinical medicine

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Professor Francesco Benedetti emerges in this Genomic Press Interview as a passionate scientist-clinician whose career has been dedicated to reclaiming psychiatry's place within medical science through rigorous research and compassionate practice. As founder and leader of the Psychiatry & Clinical Psychobiology research unit at IRCCS Ospedale San Raffaele in Milano, Italy, Dr. Benedetti has spent decades bridging the gap between neuroscience and behavioral disorders while maintaining an active clinical practice treating patients with mood disorders. His scientific journey began with a profound awareness of mental illness suffering during childhood and was shaped by his conviction that psychiatric conditions are fundamentally biological rather than merely "functional"-a controversial stance in Italian academia during his early career. Despite facing rejection from traditional psychiatric training programs, Dr. Benedetti persevered through an alternate path that ultimately led him to groundbreaking work in chronotherapeutics, immuno-psychiatry, and psychiatric genomics. Direct clinical observations have driven his research: noticing patterns of infection and inflammation in depressed patients sparked his exploration of immuno-inflammatory mechanisms; witnessing the suffering of suicidal bipolar patients unresponsive to standard treatments led to innovative chronotherapeutic protocols. Dr. Benedetti has maintained throughout his career that scientific research and clinical practice are inseparable, stating, "I see no boundaries between science and everyday clinical work." His current focus on how gene variants, immune responses, and life experiences interact to affect brain homeostasis reflects his commitment to understanding mood disorders as legitimate medical conditions rather than the "horrible abyss of pain, stigma, misery that they are now." When not conducting research, Professor Benedetti satisfies his "voracious curiosity" through reading, music, museum visits, and outdoor activities, approaching both his professional and personal life with the philosophical depth captured in his guiding motto from Ecclesiastes: "Whatever your hand finds to do, do it with all your might."

#### Part 1: Francesco Benedetti – Life and Career

**Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?** During my childhood, I became aware of the suffering associated with mental illness. I have always been fascinated by human nature. When in high school, I considered science a modern philosophy and medicine the most appropriate method to study what man is. And so, when in medical school I stumbled upon psychobiology, I deeply enjoyed its research perspective. It provided the scientific and methodological framework to in-

vestigate the physiology of behavior and potentially the origin of mental illness. The rest came by itself.

Years later, when I entered the staff of a psychiatric ward, I teamed up with colleagues who shared what I still consider my mission, seeing no boundaries between science and everyday clinical work. Some twenty years later, I became the leader of the research program in psychiatry and clinical neuroscience in the same research hospital. I am still happy to do what I can to bring psychiatry back into the house of medicine and alleviate the horrible burden of pain that patients must face.

# Please share with us what initially piqued your interest in your favorite research or professional focus area.

Most of my specific research interest stemmed from my clinical practice with patients. I remember wondering, when I was a young psychiatrist, why I was seeing rare autoimmune diseases I had never heard of, why I was routinely facing infections and pneumonia in the ward, as if patients had anomalous immune responses, why recovered patients with mood disorders told me that everything was going fine, until they got a fever, and relapsed: that was how immuno-psychiatry started, for me. Moreover, recently, when we were studying immune-inflammatory setpoints and their effects on the depressed brain, we described post-COVID depression because I predicted detrimental behavioral effects of the long-lasting inflammation associated with the infection, and I deployed me and all the researchers in my unit in the clinical services, visiting the survivors and studying them.

The need to achieve rapid therapeutic effects in acutely depressed, suicidal patients with bipolar disorder, not experiencing benefits from antidepressant drug treatments (and historically excluded from antidepressant drug trials) pushed us toward chronotherapeutics, defining new protocols combining environmental stimuli (light, dark) and manipulations of the sleep-wake rhythm for treating acute depresson, and fostered my ongoing study of chronobiology of psychiatric conditions, temporal dynamics in brain and behavior, and rapid changes in the brain paralleling rapidly changing mood states. That was my first commitment to psychiatric research, shaping my vision of how neuroscience research and clinical aims can be harmonized. I am still travelling in lecturing tours, teaching to my colleagues how to use the techniques that we developed in the 90's, aware that we did something useful to improve clinical practice, and in the meantime described the effects of genetic variants of core components of the clock machinery (GSK-3 $\beta$ , CLOCK, hPER3) on human behavior and brain structure and function.

And so, the study of gene variation and brain imaging always was, for me, a method to explore pathways involved in disease, also aiming at personalizing medical interventions, both things deeply needed because of the poor efficacy of the treatment options that we can offer to the patients, and of our poor understanding of the pathophysiology of their condition. I could not directly measure analytes in the brain of





patients, but if functional polymorphisms impact brain and behavior, I feel confident that the pathways they affect are important. I see that many of the gene variants we showed can shape the individual response to antidepressant treatments and lithium, and the course of illness (serotonin promoter, 5-HT<sub>2A</sub>, COMT, GSK-3 $\beta$ ...) are now offered to the patients in pharmacogenetic screening packages by many clinics. We did it first and never patented anything because we liked it this way.

Following our curiosity we described the interaction of genes and treatment in changing brain structure and the neural responses to stimuli when returning to euthymia, or still dwelling in the abyss of depression; and of gene variation on brain homeostasis, mainly focusing on white matter disruption, which seems a most sensitive marker of the detrimental interaction of unfavourable genomic assets, exposure to adverse childhood experiences, low-grade inflammation, and post-infection effects. Some thirty years after witnessing infections and inflammation fostering mental illness, I could show measures of brain integrity detrimentally affected by immuno-inflammatory mechanisms, metabolic dysfunctions, and gene variation affecting neurotransmitters.

This research perspective seems endless. When I look at the exponential progress in neuroscience in these years, I feel that modern psychiatry is still in its infancy, there are vast unexplored prairies in front of us: and so I keep on, observing the patients, asking questions, using the new methods that become available (at least, those that I can understand...) to try to find answers. I realize that by following our curiosity in understanding illness and improving treatments, we did some breakthrough advancement in the clinical psychobiology of mood disorders, thus defining new questions and opening new ways to address them, and seeing other researchers building up on it to increase benefits for the patients is the best reward I can think of (see me in my hospital, before a flowered wall curated by the patients, in Figure 1).

#### We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

That is sadly a fact of the Italian academic scene, that research could be considered an annoying burden by influential professors. I entered the most outstanding Italian "IRCCS", a research hospital funded by the Ministry of Health to advance knowledge and treatment options. As a staff psychiatrist, working on everyday clinical duty in the ward, I was good at it, spending most of my time trying to convert my clinical observations into research questions. We had weekly discussions about our clinical research activities and how they could improve our practice. We were physician scientists, with no preoccupation for academia. The department chair and my colleagues agreed to reduce my clinical duties to give me more time to finalize projects, thus allowing me to interact with the international scientific community in congresses (yes, at those times congresses where expected to disseminate new unpublished findings, and to foster scientific collaborations) and draft international projects.

Then, I started winning European Community and Italian MoH-funded grants, which enabled me to found my research unit at the newborn Division of Neuroscience in my hospital. That was the turning point. What now warms my heart is that most of the PIs of our ongoing granted projects were my PhD students and are now my fellow researchers.

More recently, at age 52, I also became an associate professor of psychiatry. I felt the need to share what the scientific community has learnt about mental illness with as many people as possible, also aiming at reducing the stigma associated with it, by showing that all in all, it is illness, deeply rooted in our body malfunction, as it happens in every other branch of medicine—another endless commitment, I guess.

# What is a decision or choice that seemed like a mistake at the time but ended up being valuable or transformative for your career or life?

I graduated in medicine with full marks and honors, with several papers already out. At the same time, in the medical school, I faced the psychodynamic-psychosocial-sociopolitical paradigm reigning supreme in most Italian universities, with famous professors babbling that mental illness is "functional", whatever it might mean. Patients have nothing





Figure 1. Francesco Benedetti, MD, IRCCS Ospedale San Raffaele, Milano, Italy.

wrong with their brains. Depression could be interpreted as the byproduct of a degenerated bourgeois society, or of some ill-defined unconscious psychosexual conflict. My vision was opposite, and this was not a secret.

Now, this seems like middle-aged obscurantism, but it was just some three decades ago, when my applications kept being rejected by postgraduate training schools in psychiatry, until I entered (irony: but I had to make ends meet, and I needed a certification) the neglected biological psychology branch of an unpaid residency program in Clinical Psychology, considered rather unattractive for physicians.

I could discuss my ideas with excellent therapists, learn their views, and enter the research hospital, where I am still working, for an internship. That rather desperate choice eventually allowed me to meet my colleagues, win grants, build my research team, and achieve my aims. Heterogony of ends, they call it.

#### What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

There is nothing new; I just confirmed a general rule: never betray the truth, which we aim to do. Consequently, we should never consider our research work a paid job (we are not employees; we get paid for enjoying ourselves doing what we like most) and strictly avoid conflicts of interest.

## Please tell us more about your current scholarly focal points within your chosen field of science.

I am currently spending most of my efforts investigating immunoinflammatory mechanisms in the etiopathogenesis of mood disorders, as triggered by exposure to life events and pathogens, moderated by genes, and eventually impairing brain homeostasis. All mechanisms also

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make females more prone to depression, due to the yet poorly explored interaction between hormones, the immune system, and chronobiological mechanisms. In this, I am moving from the (still valid) study of single gene variation, to polygenic scores and gene expression, always keeping brain imaging as the key method to reveal their biological effects of interest: under the assumption that gene variants (possibly conferring great advantages to humans at some point in our history) will now make some individuals more susceptible to the psychiatric effects of the above interactions between multiple factors. This assumption should not be considered trivial because it should be validated in everyday clinical work, which currently is not, and used to predict the individual risk for depression and specific outcomes reliably, and open new fields for targeting treatments.

## What impact do you hope to achieve in your field by focusing on specific research topics?

To contribute to understanding the etiopathogenesis of mood disorders, so making them yet another annoying, albeit severe, medical illness that mankind has to face, and not the horrible abyss of pain, stigma, and misery that they are now. Maybe, to contribute to find a cure, not messing up with a couple of neurotransmitters, but finally aiming at some sound pathogenetic mechanism (as we recently did by stimulating the immune system with low-dose interleukin 2: it might have seemed madness when we wrote the experimental protocol, but it was a specific intervention, based on sound previous clinical research, predicted to cause antidepressant effects, and it worked). And then, in some eleven years I will be retired: I have never been looking for fame, fortune, and glory, and now I am continuing on my way, hopefully paving the way for future researchers in this field, as others have done for me.

## What do you most enjoy in your capacity as an academic or research leader?

A relative freedom to choose in which direction to invest the research effort, paid at the price of spending much time on paperwork and other annoying commitments. Moreover, teaching is a great privilege to be chosen to share with my students what I think is best for them to know.

#### At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that you feel strongly devoted to?

Medical misogyny and disregard for the long-term effects of adverse childhood experiences. Women get depressed because they are weak, physically and morally unstable, ready to complain about nothing, easily affected by unconscious conflicts that bias their reasoning, describing dubious traumatic experiences to seek attention, etc. *Tota mulier in utero* ("the essence of woman is in the womb"), said the medieval theologian, and the concept of hysteria is still well alive in the clinics, with conditions specific to women's health – including psychiatric complaints – often dismissed. Hard to believe, suicide is the first cause of postpartum death in the "civilized" world. This attitude multiplied the stigma and has influenced research as well. I am doing what I can to change this obscene gaslighting.

# Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

I have a voracious curiosity that I satisfy whenever possible. I read a lot, listen to music, and keep visiting museums, art exhibitions, and towns. And then outdoor activities, which I am progressively reducing because of age and the ravages of time, but I still swim in alpine lakes on the sunny weekends. On summer leave, I enjoyed hiking in the Alps. Now, I prefer biking to the Tuscany seashore, and all this with my family. (See a picture of me when visiting Brugge with my wife in Figure 2).



**Figure 2.** Francesco Benedetti immersed in visual art and music at Musea Brugge, January 2025, embodying his philosophy of satisfying his "voracious curiosity" through museum visits and cultural experiences.

## Part 2: Francesco Benedetti – Selected questions from the Proust Questionnaire<sup>1</sup>

What is your most marked characteristic? Commitment, coupled with awareness.

Among your talents, which one(s) give(s) you a competitive edge? An innate ability to think out of the box, and the readiness to sacrifice everything for what I believe is worth.

<sup>1</sup>In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.



#### If you could change one thing about yourself, what would it be?

I continue to remind myself what my wife and my daughter tell me: "Take it easy." At least, sometimes I try to.

#### What is your current state of mind?

Cold as the winter wind.

#### What is your idea of perfect happiness?

A concept nearly not applicable to the living, but a surrogate could be creative apperception.

#### When and where were you happiest? And why were so happy then?

Best memories usually build up on the strong emotions we have in the broad field of our social life, and I am no exception. Some privacy here, please.

#### What is your greatest fear?

Perfectly aware of possible misunderstanding, and even a bit self-booing myself, I fear nothing.

#### What is your greatest regret?

Sometimes I told myself that I could have enjoyed more the so-called "pleasures of life", but all in all, my pleasure is in using my brain to (try to) cultivate my spirit, and do what I am doing, my way.

#### What are you most proud of?

Just having done what I did, trying to do the best I could. Could it have been done better? Of course.

#### What do you consider your greatest achievement?

I always look ahead, using scientific achievements as bricks to climb on. I do not know what to mention: my next finding.

#### What or who is your greatest passion?

Science. When I take professional stuff as personal, it is because it is really difficult for me to see a difference.

#### What is your favorite occupation (or activity)?

When I am not conducting research, reading, or immersing myself in music and visual arts, my mind wanders toward the unspeakable.

#### What is your greatest extravagance?

Living? No rationale in it.

What is your most treasured possession? My brain.

Where would you most like to live? On a seashore.

What is the quality you most admire in people? Sincerity.

What is the trait you most dislike in people? Hypocrisy.

What do you consider the most overrated virtue? Kindness.

What do you most value in your friends? Sincerity.

Which living person do you most admire? Not a name, but a type, the meek.

#### Who are your heroes in real life?

The people who struggle with their loved ones in the wars now devastating the planet, trying to salvage some moral principles, humanity, some reasons to believe that not everything will be lost.

## If you could have dinner with any historical figure, who would it be and why?

A tragic figure, Marcus Aurelius Antoninus. "Short, therefore, is man's life, and narrow is the corner of the earth wherein he dwells" (as quoted in Maugham): a sentence by one of the mightiest emperors of the Roman empire, a warrior, a philosopher writing on the same essence of moral philosophy, his reasoning so fresh now as nearly two thousand years ago. Among physicians, I would find a kindred spirit in Ernest Septimus Reynolds, whose 19<sup>th</sup>-century paper summarizing his experience on the occurrence of mental symptoms in bodily disease, gained through close observation of the patients at the Manchester Workhouse Infirmary and Lunatic Wards, is still inspirational to me. I want to ask him a couple of questions; I think he could give me some good advice for life and my profession.

#### Who are your favorite writers?

Oh well, they changed so many times along the trajectory of my life. But to say one name, Giacomo Leopardi.

#### Who are your heroes of fiction?

Odysseus.

#### What aphorism or motto best encapsulates your life philosophy?

A line from Ecclesiastes 9:10: "Whatever your hand finds to do, do it with all your might, for in the realm of the dead, where you are going, there is neither working nor planning nor knowledge nor wisdom." I keep my hands busy, and seeing what lies beyond that darkness would be nice.

Milano, Italy 7 May 2025

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