The Milano Project

Mapping the Basic Science of Post-Finasteride Syndrome to Identify Potential Therapies for an Emerging Epidemic

A three-year research initiative by the University of Milano Department of Pharmacological and Biomolecular Sciences, sponsored by the Post-Finasteride Syndrome Foundation.

April 8, 2024

The Emerging Epidemic

Post-finasteride syndrome (PFS) occurs in patients who've taken finasteride, a 5-alpha reductase type II enzyme inhibitor used to treat hair loss (under the brand name Propecia or generics) and/or enlarged prostate (Proscar or generics). Symptoms, which are persistent—and, in some cases, appear to be permanent—manifest themselves in three realms:

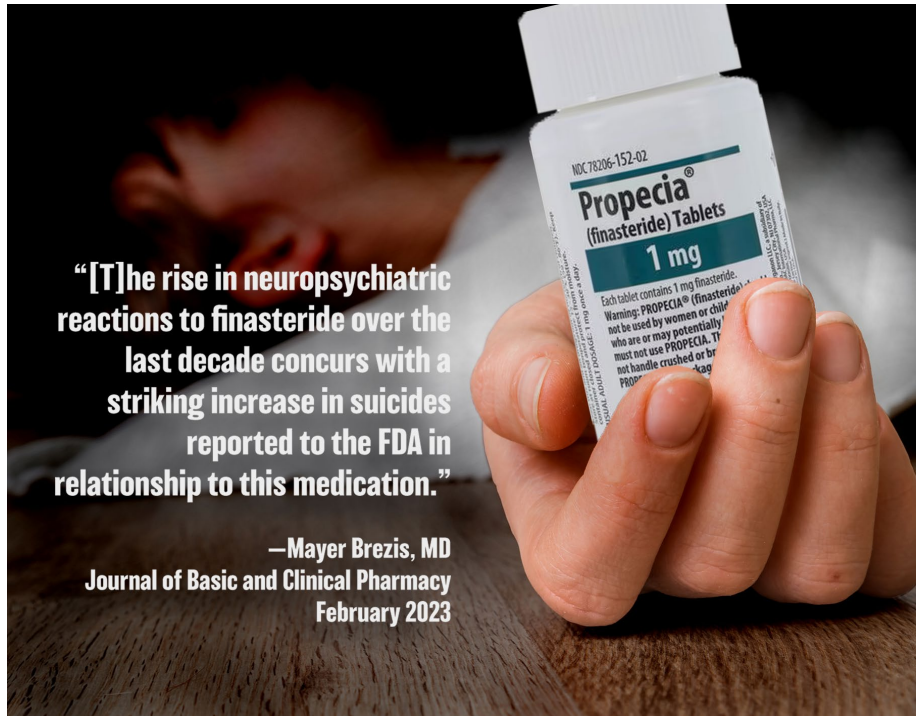
• **Sexual**, such as erectile dysfunction, loss of libido, ejaculation disorders, testicular pain, genital shrinkage, and Peyronie's disease;

• **Physical**, such as gynecomastia, muscle disorders, dry skin, chronic fatigue, tinnitus, and diabetes; and

• **Psychological**, such as depression, anxiety, insomnia, cognitive dysfunction, suicidal ideation, and suicidal behavior.

According to Google Analytics, more than 825,000 unique users have visited the PFS Foundation website since its 2012 launch. Conservative estimates based on data from a 2017 study titled Persistent erectile dysfunction in men exposed to the 5α-reductase inhibitors, finasteride, or dutasteride, and from Merck & Co.'s market data uncovered in the Propecia mass-tort litigation, indicate there are more than 100,000 PFS patients worldwide.

Increasingly Characterized by Suicide



More alarming, a subset of PFS patients have, as an apparent result of the condition, taken their own lives. According to data in the World Health Organization's VigiBase database of adverse drug reactions (ADRs), 575 deaths have been attributed to finasteride use, 101 of which are suicide cases.

The epidemiology on PFS suicides is now clear enough that:

• In 2022, the US Food and Drug Administration mandated that a suicidality warning be added to the finasteride 1 mg product label.

• That same year, France's FDA counterpart, ANSM, mandated that a "red-box" warning be added to all finasteride 1 mg products.

• In 2023, Canada's Health Canada, completed its fourth safety investigation into the drug, finding that 23 suicide cases were "found to be possibly linked to the use of finasteride." The agency thus recommended that all finasteride patients "be screened for suicidal ideation, self-harm, and depression and/or associated risk factors before treatment initiation."

• Also in 2023, Japan's Pharmaceuticals and Medical Devices Agency conducted a disproportionality analysis, which showed that finasteride-precipitated suicides were 270% higher than would be expected.

• That same year, the UK's MHRA, launched its first-ever safety investigation into finasteride. Its results are scheduled for release in 2024.

The Problem, Patient-wise

There is no scientifically proven therapy for PFS. That fact alone, according to hundreds upon hundreds of case reports filed with the PFS Foundation, often drives PFS patients to suicidal behavior. And more frequently, they're succeeding.

According to a recent analysis of suicidality reports for finasteride within the FDA's Adverse Event Reporting System (which include suicide attempts, suicidal behavior, suspected suicide, and completed suicide), the number of such reports rose 375% from 2019 to 2020, totaling 95 that year. None of which came as a surprise to us.

On Nov. 7, 2013, **Daniel Stewart**, 37, a Professor of Criminal Justice at the University of North Texas, wrote us: "But for your efforts providing hope, I probably wouldn't be alive today. Six months ago (after taking only 9 Propecia pills), I found myself afflicted with PFS, and since then my life has been fundamentally altered." On April 12, 2014, Daniel was dead by his own hand.

On April 4, 2022, **Marc Turner**, 36, a ranger with the Parks and Recreation Department in Mississauga, Canada, wrote us: "I was heavily influenced into thinking finasteride was safe by misinformation on YouTube." On April 13, 2022, Marc took his own life.


Marc Turner: 1985-2022

In the eight years between those two PFS suicides—during which we were informed directly of a dozen more such suicides—major progress had been made in terms of PFS medical awareness, media awareness and regulatory awareness.

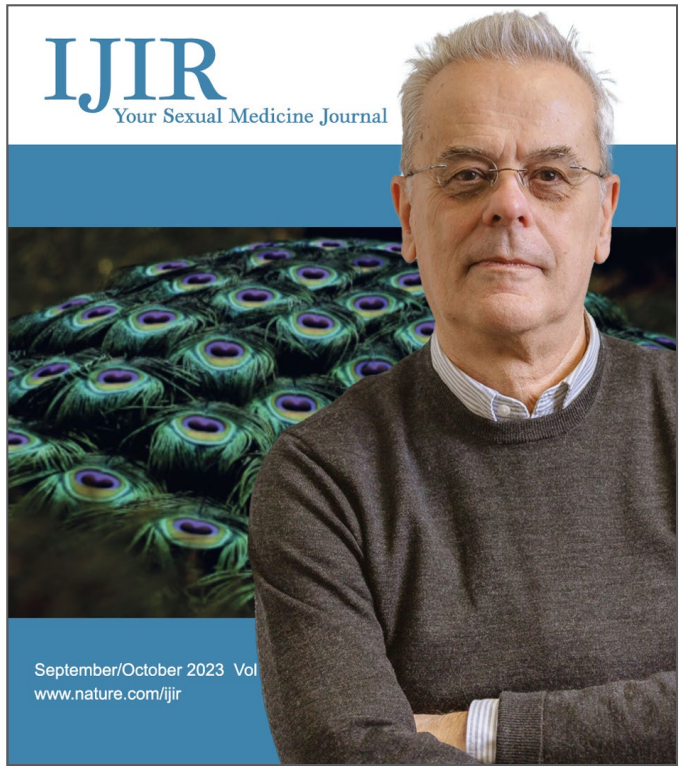
But for PFS *patients*, none of that mattered. Because there were still no effective therapies for the condition. And while most PFS patients are not driven to suicide, the majority of them report decimated professional, familial, and social lives, as they're left praying for therapies that may or may not materialize in their lifetime.

The Science Man with a Plan

For more than a decade now, **Roberto Cosimo Melcangi**, PhD, Head of the Neuroendocrinology Unit in the Department of Pharmacological and Biomolecular Sciences at the University of Milano, has been investigating PFS at the molecular and genetic levels. During his 40-year career, Prof. Melcangi and his research teams have published more than 200 studies in high-impact-factor medical journals. Among them, 14 have focused on PFS:

- Neuroactive steroid levels are modified in cerebrospinal fluid and plasma of PFS… The Journal of Sexual Medicine, 2013
- Adverse effects of 5α-reductase inhibitors… Reviews in Endocrine and Metabolic Disorders, 2015
- Patients treated for male pattern hair with finasteride show, after discontinuation… Journal of Steroid Biochemistry, 2015
- Effects of subchronic finasteride treatment and withdrawal on neuroactive steroid levels… Neuroendocrinology, 2016
- Neuroactive steroid levels and psychiatric and andrological features in PFS… Journal of Steroid Biochemistry, 2017
- Treatment of male rats with finasteride, an inhibitor of 5alpha-reductase enzyme… Psychoneuroendocrinology, 2019
- Altered methylation pattern of the SRD5A2 gene in cerebrospinal fluid of PFS… Endocrine Connections, 2019
- Alterations of gut microbiota composition in PFS… Journal of Endocrinological Investigation, 2020
- Post-finasteride syndrome: An emerging clinical problem Neurobiology of Stress, 2020
- Three-Dimensional Proteome-Wide Scale Screening for the 5-Alpha Reductase… Journal of Medicinal Chemistry, 2021
- Gut Inflammation Induced by Finasteride Withdrawal Therapeutic Effect of Allopregnanolone… Biomolecules, 2022
- Exploring Rat Corpus Cavernosum Alterations Induced by Finasteride Treatment and… Andrology, 2023
- Post-Finasteride Syndrome And Post-SSRI Sexual Dysfunction… Frontiers in Neuroendocrinology, 2024
- Analysis of the Finasteride Treatment and Its Withdrawal in the... Journal of Endocrinological Investigation, March 2024

"We're dealing with an iceberg situation, in which we see the tip but fail to spot what's underneath," Melcangi says of the PFS epidemic.



Proven Influencer

Prof. Melcangi's work is also regularly referenced by fellow researchers worldwide. As just 10 examples from recent years:

- Sexual dysfunction in men taking systemic dermatologic medication: A… Journal of the American Academy of Dermatology, 2019
- The potential involvement of cholinergic system in finasteride induced cognitive dysfunction Psychoneuroendocrinology, 2020
- Allopregnanolone, the neuromodulator turned therapeutic agent: Thank you, next? Frontiers in Endocrinology, 2020
- Health risks associated with long-term finasteride and dutasteride use: It's time to… The World Journal of Men's Health, 2020
- Finasteride and Suicide: A postmarketing case series Dermatology, 2020
- Risk of depression associated with finasteride treatment Journal of Clinical Psychoparmacology, 2021
- Differential gene expression in post-finasteride syndrome patients Journal of Sexual Medicine, 2021
- Diagnostic criteria for enduring sexual dysfunction after treatment with… International Journal of Risk & Safety in Medicine, 2021
- Neuropsychiatric reactions to finasteride: nocebo or true effect? Journal of Basic and Clinical Pharmacy, 2023
- The Post-Finasteride Syndrome: Possible etiological mechanisms and symptoms International Journal of Impotence Research, 2023

Significant Headway

Needless to say, Prof. Melcangi is the world's most prolific PFS investigator, to say nothing of fastest and most economical. But by several indications, his best is yet to come. In the past two years, Team Melcangi achieved three breakthroughs:

1. ID'd culprit genes

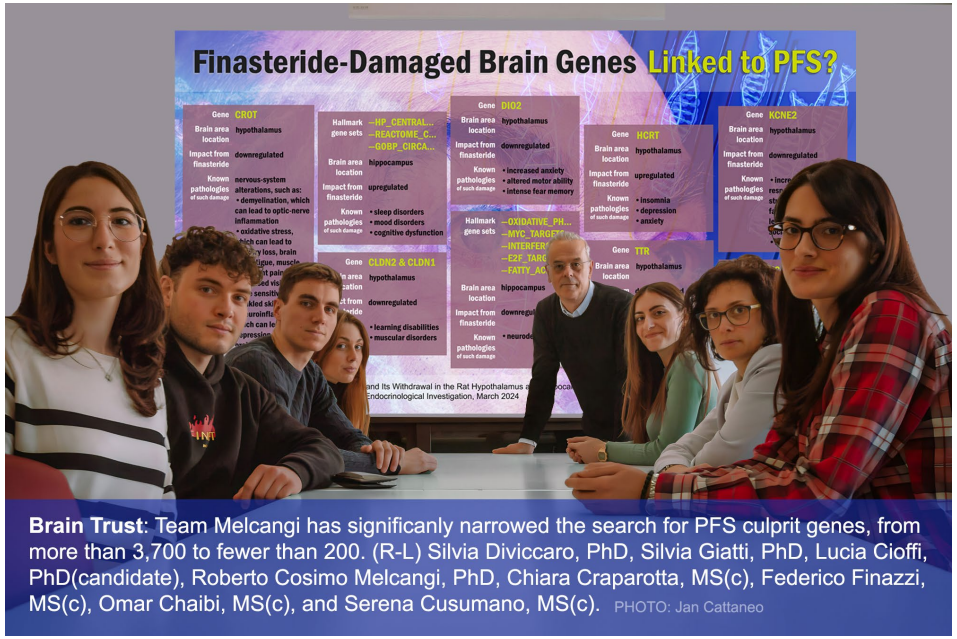
Via a next-generation sequencing technology known as RNA-seq, Team Melcangi has identified 186 brain genes that are likely linked to major PFS symptoms, including depression, anxiety, insomnia, and cognitive dysfunction That study was published in the March 2024 edition of the *Journal of Endocrinological Investigation*.

2. Discovered that finasteride ED differs during treatment vs. after quitting

In 2023, Team Melcangi published a study titled Exploring Rat Corpus Cavernosum Alterations Induced by Finasteride Treatment and Withdrawal, which showed that "finasteride treatment, but not its withdrawal," affects the penile tissues facilitating erection. In other words, PFS ED may be related to brain damage, rather than groin damage—an important distinction when searching for effective therapies.

3. Hinted at a possible therapeutic target

In 2022, Team Melcangi published a study titled, Gut Inflammation Induced by Finasteride Withdrawal: Therapeutic Effect of Allopregnanolone in Adult Male Rats. It demonstrated that the neurosteroid allopregnanolone proved effective in counteracting some of the finasteride-induced alterations in gut microbiota.



Brain Trust: Team Melcangi has significanly narrowed the search for PFS culprit genes, from more than 3,700 to fewer than 200. (R-L) Silvia Diviccaro, PhD, Silvia Giatti, PhD, Lucia Cioffi, PhD(candidate), Roberto Cosimo Melcangi, PhD, Chiara Craparotta, MS(c), Federico Finazzi, MS(c), Omar Chaibi, MS(c), and Serena Cusumano, MS(c). PHOTO: Jan Cattaneo

A Promise of Further Breakthroughs

Team Melcangi is presently immersed in two projects designed to bring PFS into further focus. Prof. Melcangi explains:

1. Follow the nerve-damage thread

“Many PFS patients report numbness and/or paresthesia (aka ‘pins and needles’) in the genital area, as well as in the limbs, and elsewhere, which suggests peripheral neuropathy (aka nerve damage). So, in our PFS experimental model, we evaluated the morphology of peripheral nerves, as well as intraepidermal nerve fiber density. Results thus far indicate that those parameters are not affected. Now, we’re evaluating other markers that have recently been reported as possible sources of genital numbness and paresthesia.”

2. Does finasteride trigger an inflammatory process?

“Our research published to date indicates that finasteride treatment, and its withdrawal, induce local inflammation of the nervous system and in the gut. On that basis, we’re evaluating whether systemic inflammation may also occur. Specifically, we want to determine how immune cells can be shaped by finasteride treatment, thus altering immune response. We’re in the process of evaluating inflammatory mediators (known as chemokines and cytokines) in finasteride-treated rats, particular white blood cells, which are critical to immune function.”

The Big Picture

In addition to the published and current research described thus far, Team Melcangi is preparing to:

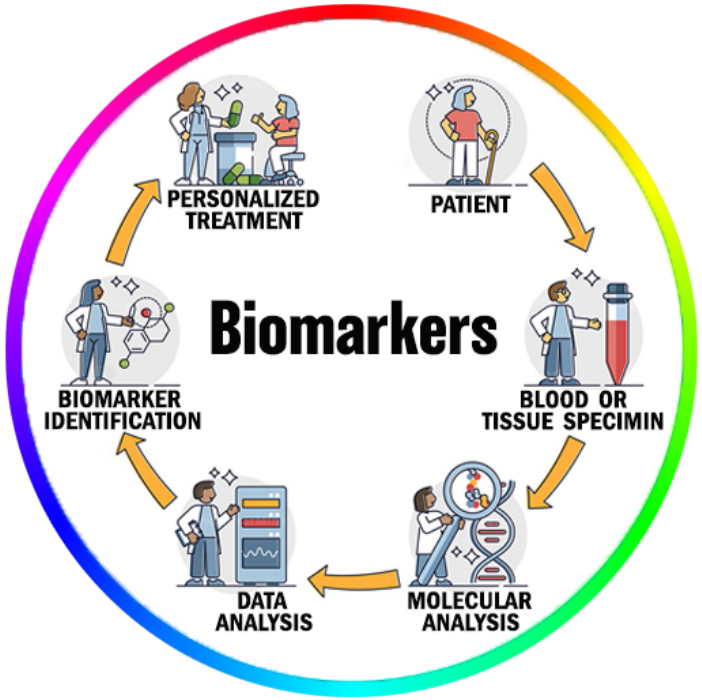
1. Establish biomarkers

"When analyzing PFS from a biomolecular perspective, many clinical endpoints and reliable biomarkers are missing. That means we don't know what damage PFS patients may have sustained, or whether an experimental therapy has yielded improvements or not," explains Prof. Melcangi.

"So, we want to explore the potential role of miRNAs in our animal model. miRNAs represent a class of small, non-coding RNAs that regulate gene expression. These molecules meet most of the criteria for being an ideal biomarker. They're already used as biomarkers in various types of cancer, cardiovascular diseases, sepsis, neurodegeneration, and nervous-system disorders. Evaluating their role in PFS will thus provide a proof of concept, which will be critical as we move from animal models to human patients in a clinical setting."

2. Explore how PFS brains irregulate sexual function

As a follow-up to their culprit-genes study, Team Melcangi will run RNA-seq analysis on genes expressed in brain areas related to sexual function and motivation, such as the nucleus accumbens. "On the basis of our published research into the differences between ED during finasteride treatment and during withdrawal of the drug, we will explore the possible brain pathways leading to sexual dysfunction," says Prof. Melcangi. "In animal models, this experiment will also involve behavioral tests to evaluate both sexual motivation and performance."



The Big Picture (cont'd)


PHOTO: Jan Cattaneo

In addition to the published and current research described thus far, Team Melcangi is preparing to:

3. Learn if finasteride-altered gut flora changes brain function

"Several published studies support the biological importance of the gut-brain axis, i.e., the two-way biochemical signaling that takes place between the gastrointestinal tract and the central nervous system. Specifically, such communication occurs via gut microbiota, and vagus nerves, which regulate internal organ functions, vasomotor activity, and certain reflex actions," says Prof. Melcangi. "Whether the microbial molecular mediators involved are negatively triggered by finasteride treatment and/or its withdrawal is still not clear. Therefore, bacteria-derived metabolites such as the short-chain fatty acids, serotonin, dopamine and other neurotransmitters will be evaluated to determine if they play any role in finasteride-induced dysregulation of brain genes."

4. Get more granular on the gut angle

"Our published research indicates that gut functionality is compromised by PFS. But despite knowing that finasteride use leads to intestinal microbial dysbiosis—a condition wherein gut bacteria becomes imbalanced, causing diarrhea, cramping, constipation, bloating, indigestion, nutrient deficiencies, chronic inflammation, allergic reactions, and/or other disturbances—how this may impact gut-brain axis is still unclear," adds Prof. Melcangi. "The next step will be to investigate if the microbiome-encoded enzymes can directly and substantially affect systemic finasteride metabolism. This could be useful in understanding the interpersonal differences in drug metabolism, which is connected to interpersonal variability in microbiomes."

One Possible Therapy: Allopregnanolone

Based on Team Melcangi's published research and data being produced by their current experiments, Prof. Melcangi plans to explore potential therapeutic effects of allopregnanolone (ALLO) in his animal model.

A naturally occurring neurosteroid made in the body from the hormone progesterone, ALLO can repair and protect central nervous system functions, act as an antidepressant, and reduce anxiety.

ALLO is currently being used to effectively treat postpartum depression.

Team Melcangi will thus explore ALLO's effects on genes and signal pathways identified in their recently published PFS culprit-genes study. Additionally:

- ALLO's effect on gut microbiota and the gut-brain axis altered by finasteride treatment and withdrawal will be tested.
- If new markers for genital numbness and paresthesia are confirmed, they will be considered for ALLO testing.
- If it turns out that finasteride induces systemic inflammation, ALLO will be tested as a therapy.

The Research

The Milano Project is comprised of 7 studies, all of which will be conducted by Team Melcangi researchers, and overseen directly by Prof. Melcangi. Additionally, all research will be conducted onsite at the University of Milano's Department of Pharmacological and Biomolecular Sciences in Milano, Italy, with a target completion date of December 31, 2026.

7 Investigations	Time to complete (estimated)
1. Brain Therapy Exploration: The next step in our recently published brain-genes research (Analysis of the Finasteride Treatment and Its Withdrawal in the Rat Hypothalamus…) will be to explore potential therapeutic effects of ALLO on the culprit genes and signal pathways identified in that study.	6 months
2. Tactile-Sense Therapy Exploration: Assuming we identify the neurological source(s) of genital numbness and paresthesia in PFS patients (our investigation into which is currently under way), we will explore the potential therapeutic effects of ALLO on those dysregulated genes and signal pathways.	6 months
3. Gut Therapy Exploration: This study involves two elements that should and will run concurrently, due to overlaps in biological targets and investigative methodologies: (a) We will analyze ALLO's effect on the gut microbiota and gut-brain axis altered by finasteride treatment and withdrawal. (b) We will evaluate microbial molecular mediators—namely, bacteria-derived metabolites such as serotonin, dopamine, short-chain fatty acids (SCFA), and other neurotransmitters—to determine if they can affect brain function. If so, we will begin exploring correlations between those mediators and PFS symptoms.	12 months

The Research (cont'd)

7 Investigations	Time to complete (estimated)
4. Immune Response Therapy: Our published observations indicate that finasteride treatment and its withdrawal induce local inflammation in the nervous system and gut. We are thus evaluating whether systemic inflammation may also occur. As such, we are investigating how immune cells can be shaped by finasteride treatment and thus altering the immune response. In particular, the inflammatory mediators (i.e., chemokynes and citokyes) will be evaluated in ex vivo splenic macrophages from finasteride-treated rats. Assuming this current research demonstrates systemic inflammation, will explore the potential therapeutic effects of ALLO on the respective immune cells and their genetic pathways.	12 months
5. Molecular Biomarkers: We will explore the potential role of miRNAs, which regulate gene expression, in our animal model. miRNAs are already used as biomarkers in various types of cancer, cardiovascular diseases, sepsis, and nervous-system disorders. Evaluating their role in PFS will provide a proof of concept, which in turn will be critical as we move to human patients in a clinical setting.	6 months
6. ED Therapy Exploration: Our published observations (Exploring Rat Corpus Cavernosum Alterations Induced by Finasteride Treatment and Withdrawal) demonstrated that the type of sexual dysfunction experienced by patients during finasteride treatment differs from the type of sexual dysfunction that persists post-treatment. We will thus explore potential therapeutic effects of ALLO on the culprit genes and signal pathways identified in that study.	10 months
7. Psychological Biomarkers: Concurrent with examining PFS at the molecular level, as outlined in the 6 studies above, we will explore motivation and depressive-like behavior in our animal model. Data obtained through these behavioral tests will help identify which areas of the brain are chiefly involved in various PFS symptoms. That will in turn provide a roadmap of which tissues to focus on in subsequent molecular analyses.	12 months

Note: We are targeting a completion date for the Milano Project of December 2026, assuming it is fully funded by June of that year. However, 2 of the 7 planned studies have already been launched, which is why we estimate 3 years total worth of work, instead of 2 years and 7 months. Additionally, the cumulative time to complete this project runs 5 years and 4 months, but several of the studies will be conducted concurrently, thus resulting in a total project span of less than 3 calendar years.

Team Synergy

One of Team Melcangi's greatest assets is their ability to cross-pollinate and, when necessary, quickly pivot. In other words, having the same group of 10+ researchers working on various studies in the same physical lab allows them to discuss progress daily, share new data as it emerges, and develop new hypotheses accordingly.

That synergy, vis-à-vis PFS, exists in just one place on earth: the University of Milano's Department of Pharmacological and Biomolecular Sciences.

Fast-Track Funding Drive

Up until now, Team Melcangi has relied on sporadic, piecemeal funding from various sources including the PFS Foundation. And to their credit, they've done an excellent job of publishing a body of medical literature that has influenced—and continues to influence—not only fellow researchers, but drug-regulatory authorities, the legal community, members of the media, health care providers, and men considering finasteride therapy.

But to fast-track efforts aimed at (a) mapping out the basic science necessary to move from an animal model to human clinical trials, and (b) providing drug-regulatory authorities with enough scientific evidence to remove finasteride from the market—or at least significantly tighten controls on the drug—we believe it's critical to fund all seven of Team Melcangi's investigations via one concerted effort.

The good news is, $300,000, just $43,000 per study—a small sum by research standards—will get the job done. Better still, we've already raised $30,000, so our target is now just $270,000 over the next 30 months. Specifically, that sum will:

• Allow Prof. Melcangi and his research team to work full-time on the Milano Project through the end of 2026, and

• Cover the cost of all the current and planned studies laid out in this proposal.

Thank you for your consideration of this significant contribution to medical science.

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PFS FOUNDATION

Finasteride
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