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Short Communication

# Sex-Specific Signaling: The Role of COX-2/CREB/ER in Male Susceptibility to Pulmonary Fibrosis

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## DESCRIPTION

Nowhere is this more evident than in Idiopathic Pulmonary Fibrosis (IPF), a lethal lung disease where the immune system triggers runaway scarring. Historically, men have been diagnosed with IPF at significantly higher rates and with worse outcomes than women. For decades, this was blamed on smoking or occupational hazards. However, we now know the true "root" is a sex-specific signaling axis involving testosterone and Estrogen Receptors (ER) that makes the male immune system uniquely vulnerable to lung destruction.

This discovery is a landmark for "gender-aware" medicine. It suggests that a remedy that works for a woman may be entirely ineffective for a man because the biological "wiring" of their immune-fibrotic response is fundamentally different.

The biological roots of this sex bias are found in the lung's resident macrophages the "sentinel" cells of the immune system. In both sexes, lung injury triggers these macrophages to release inflammatory signals. However, the way these signals are processed depends on the presence of Estrogen Receptors (ER). In women, high levels of estrogen acting on ER-beta provide a natural "brake" on the inflammatory enzyme COX-2. This prevents the activation of a protein called CREB, which is the master switch for collagen production.

In men, the lack of this estrogen "buffer" means the COX-2/CREB pathway is "wide open." When a male lung is exposed to a trigger be it a virus or pollution the macrophages over-respond. They produce a massive amount of CREB-driven signals that tell the lung's fibroblasts to start building scar tissue. The male immune system, in this context, is "hyper-fibrotic." This isn't just a matter of hormones; it's a matter of how those hormones program the immune cells' Deoxyribonucleic Acid (DNA) has that male macrophages have a distinct "epigenetic signature" that makes them prone to this pro-fibrotic state. This is the biological root of why men succumb to IPF faster: their immune systems are "pre-programmed" for a more aggressive scarring response.

### ER-beta agonists and male-specific fibrotics

The remedy for this sex-specific vulnerability is the development of "Selective Estrogen Receptor Modulators" (SERMs) designed specifically for the male lung. In 2025, clinicians are using inhaled ER-beta agonists that deliver the protective "estrogen signal" directly to the lung macrophages without causing systemic feminizing effects. This "tricks" the male immune system into behaving like a female immune system, activating the COX-2 "brake" and silencing the CREB-driven scarring process.

Clinical precision is further refined by "macrophage reprogramming." Using nanoparticle delivery systems, doctors can deliver "CREB-silencing" RNA directly to the immune cells in the lung. This stops the fibrosis at its molecular root before the scarring becomes irreversible. For male patients, this is a life-saving shift. Instead of using broad anti-fibrotics that only slow the disease, we are using sex-specific remedies that address the underlying hormonal-immune imbalance. This approach acknowledges that the lived experience of disease is different for men and women, and that our remedies must reflect that biological reality.

## CONCLUSION

The identification of the COX-2/CREB/ER axis marks a new era in the treatment of pulmonary fibrosis. By addressing the biological roots of male susceptibility, we have moved beyond "general" lung care to a "sex-specific" precision model. This ensures that men are no longer at the mercy of their biological wiring, but are instead provided with remedies that are as unique as their own genetic and hormonal profile.

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