Dispute Surfaces Over Paternity of RU 486

Etienne-Emile Baulieu is credited with getting the pill into clinical practice, but Roussel scientists say they discovered it

"ETIENNE BAULIEU is the father of the pill, but he is not the father of the compound." So says Georges Teutsch, a chemist in the Department of Endocrinology at the French drug company Roussel Uclaf. The pill is the widely touted abortion pill. The compound is RU 486.

Just who made the key contributions to the development of RU 486 has become a matter of contention since September when Baulieu won the Lasker Prize for his role in bringing the pill into clinical practice. In a profile published in this journal in September (*Science*, 22 September, p. 1323), Baulieu said that researchers at Roussel would have missed the significance of RU 486 had it not been for his input and guidance. In a letter on page 985, Teutsch laconically remarks that Baulieu's story "does not fit the facts as I recall them." Reminded of his claim by *Science*, Baulieu said simply: "I still believe [it]."

The issue is one of history and credit: Baulieu's account of a discovery that may prove worthy of a Nobel Prize casts himself as composer and conductor. Others played their parts, but it was his score. The bit players, however, stress their creative role.

Everybody agrees that Teutsch made an important contribution in 1975 when, "more or less by fiddling," as he recalls, he found a new way of creating chemical variations on the basic steroid molecule. The systematic synthesis of these analogs fell to Alain Belanger, a Canadian postdoc at Roussel, and some of the new compounds seemed able to block steroid receptors.

In 1979, because Roussel had chosen to steer clear of sex hormones—in a Catholic country, that was considered prudent and ethical—the company invited outside consultants to meet with researchers and dream up promising projects on "nonsexual steroids." One of the consultants was Baulieu. The other was Derek Barton, now a professor of chemistry at Texas A&M.

"We were discussing anti-everything," Barton recalled, but work on anti-sex hormones was out of the question because of Roussel's policy. The company settled on anti-glucocorticoids, perhaps because one of Teutsch's first compounds, RU 25055, showed signs of blocking corticosteroids.

Analogs of RU 25055 went to Daniel Philibert, the biologist in charge of anti-glucocorticoid research. He assessed each against a panel of five steroid receptors. The fourth compound in the series was RU 486. "We were surprised by the very high affinity of RU 486 to the glucocorticoid and progesterone receptors," Philibert explained, but at that time they did not know whether the compound would be an agonist or an antagonist—a mimic or a blocker—of the relevant hormones.

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There were reasons to assume it would not be a blocker. Jean-Pierre Raynaud, Philibert's first boss at Roussel and an endocrine biologist, had proclaimed a theory linking binding profile to function: hormones bind to their receptors and dissociate from them in a continual dynamic dance; those that split quickly would be blockers, while those that stayed bound longer would be mimics, Raynaud believed.

Baulieu said that work in his laboratory convinced him that Raynaud was wrong; high-affinity compounds could be pure antagonists. Furthermore, if the Roussel researchers had followed the reasoning of Raynaud, their chief, they would have ignored high-affinity compounds in the search for anti-hormones. Baulieu says he told Roussel to "check the high-affinity compounds," and thus did they stumble on RU 486's properties.

Philibert, however, insists that Baulieu did not mention this to the Roussel team. Baulieu responds: "I didn't mention it [to Teutsch] because I did not have to. But I did mention it to [Jacques] Boissier and Raynaud," researchers above Teutsch and Philibert on the company ladder. Very early in the story, "around '76," he went to Raynaud and said, "Jean-Pierre, you're wrong." For Baulieu, the issue is one of hierarchy. Most of his meetings were with the chief scientists at Roussel. They may or may not have passed his suggestions down the line.

But having been surprised by RU 486 binding tightly to the glucocorticoid and progesterone receptors, the Roussel researchers—with no guidance from Baulieu, they say—decided to investigate further.

RU 486 did not mimic glucocorticoids, whatever Raynaud had prophesied. In fact, it completely blocked their effects. This was in June 1980. "So we had a compound with high affinity that was an antagonist," Philibert recalled. The compound also had high affinity for the progesterone receptor. The next step was obvious: "We tested immediately [for progesterone and] anti-progesterone activity in vivo." Again, the compound came up trumps; it completely impeded the normal effects of progesterone.

Teutsch says that when Baulieu was told that they had a high-affinity potent anti-glucocorticoid, "Baulieu said that Roussel Uclaf should confirm the anti-glucocorticoid activity in humans." The compound was sent off for toxicity testing.

Only in March 1981 could Teutsch and Philibert tell Baulieu that RU 486 also blocked progesterone. From that point, the parallel histories of RU 486 merge. Baulieu said to Roussel: "It should be tested in people, and I can get that done."

But before that could happen, Baulieu says, he had to salvage RU 486 again. The toxicity tests had ended in the deaths of two of three monkeys. When, months after it had been sent for testing, Baulieu inquired about the drug, someone at Roussel told him, "Your compound is dead." He pointed out that the reported cause of death was exactly what they should have expected of such a potent anti-glucocorticoid in high doses for long periods. Baulieu encouraged Roussel to continue with human testing.

Teutsch acknowledges that Baulieu was "very, very useful" in the development of the drug. Baulieu persuaded Edouard Sakiz, chairman of Roussel Uclaf and an old friend, to abandon the company's stance against contraception and abortion. "If [Baulieu] had not been there," says Teutsch, "Roussel Uclaf would not have developed the compound for this indication."

So did Baulieu discover RU 486? Says Teutsch: "That's going too far."

Baulieu insists that there is more to discovering a drug than making the compound. "You have to have a use for it." His version: "Even if I'm not the father, I am . . . the godfather, because I rescued the compound." ■ JEREMY CHERFAS