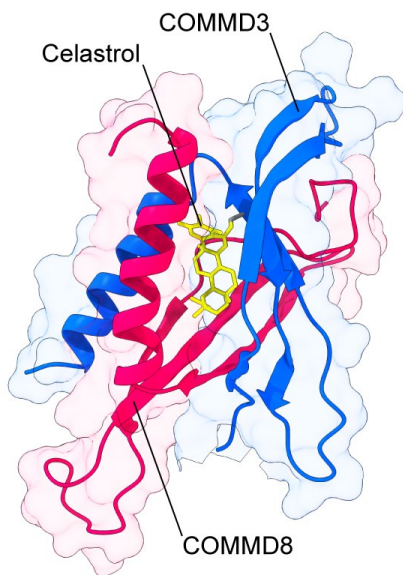


## Celastrol suppresses humoral immune responses and autoimmunity by targeting the COMMD3/8 complex

Celastrol, a bioactive molecule extracted from the *Tripterygium wilfordii* plant, has been shown to exhibit anti-inflammatory properties. However, its mechanism of action has not been fully elucidated. Taiichro Shirai, Kazuhiro Suzuki, and the research group showed that celastrol suppresses humoral immune responses and autoimmunity by disabling a protein complex consisting of copper metabolism MURR1 domain-containing (COMMD) 3 and COMMD8 (COMMD3/8 complex), a signaling adaptor for chemoattractant receptors. Having demonstrated the involvement of the COMMD3/8 complex in a mouse model of rheumatoid arthritis, they identified celastrol as a compound that covalently bound to and dissociated the COMMD3/8 complex. Celastrol inhibited B cell migration, reduced antibody responses, and blocked arthritis progression, recapitulating deficiency of the COMMD3/8 complex. These effects of celastrol were abolished in mice expressing a celastrol-resistant mutant of the COMMD3/8 complex. These findings establish that celastrol exerts immunosuppressive activity by targeting the COMMD3/8 complex. Their study suggests that the COMMD3/8 complex is a potentially druggable target in autoimmune diseases and points to celastrol as a lead pharmacologic candidate in this capacity.



**Figure: *In silico* modeling of the celastrol-bound COMMD3/8 complex**

Celastrol, an herbal medicinal ingredient, improves the pathology of autoimmune diseases by suppressing the COMMD3/8 complex.

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