S38-6 Discovery research of novel anti-gout and hyperuricemia drug

◯Shiro KONDO[1,2]

[1]Teijin Limited, [2]Kondo Laboratory

Gout is a disease associated with hyperuricemia and peculiar to human, especially adult men. Though the control of uric acid biosynthesis is effective for this disease, there is no drug except Allopurinol in the world, which was launched in 1960's. Allopurinol, an analog of purine base, has potent hypouricemic action by inhibition of xanthine oxidoreductase (XOR). Many compounds having more potent activity than allopurinol had been reported in patents and articles from 1970's, but no drug has been launched. We thought that there was another reason of the failure in development of these drugs other than adverse effects on the nucleotide metabolism due to their purine like structure. We started the research of the non-purine inhibitor on XOR with the efforts for the clarification of causes of developmental failure.

Further investigation revealed that the active form of allopurinol is oxypurinol, a main metabolite of allopurinol, and the true activity of it on XOR is nearly 1nM. On the other hand we synthesized many compounds having new scaffold and found that a series of phenylthiazolecarboxylic acid derivatives had some inhibitory activity on XOR. After the optimization based on structure-activity relationship and pharmacokinetics analysis, we had succeeded in acquisition of more potent compounds than allopurinol on hypouricemic effect in animal models. Further investigations in pharmacological and toxicological test reached TMX-67. This compound, Febuxostat, had approvals as a new drug in Europe and US, and is in preparation for application in Japan.