日本大学大学院薬学研究科入学試験問題

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英　語（基礎薬学分野）

次の３つの英文のうち，２つを選び訳しなさい.

1

The Nobel Prize winning research in the laboratories of Bloch and Lynen (1964) and Brown and Goldstein (1985) for their discoveries concerning the regulation of cholesterol levels ultimately led to the discovery of the statins. In the 1960s, evidence was growing that cholesterol levels were a major risk factor in coronary heart disease demonstrated by a 6-year follow up from The Framingham Study. Based on this research, many pharmaceutical companies began searching for inhibitors of the enzyme HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. The discoveries of compactin and mevinolin represent two of the first natural product inhibitors discovered using an enzyme assay from extracts. Endo at Sankyo collaborated extensively with Brown and Goldstein for characterization of compactin. Related molecules [e.g., simvastatin, atorvastatin] followed from these basic studies.

2

Taxol was isolated from *Taxus brevifolia* in 1971 as a cytotoxic agent with *in vivo* efficacy but was not advanced for development until the elucidation of the mechanism of action (MOA) in 1979. The molecule binds to tubulin and stabilizes the microtubule polymer protecting it from disassembly. After the MOA determination and heroic efforts by the US National Cancer Institute for large-scale isolation and clinical evaluations, the compound was licensed by Bristol Myers Squibb for development and commercialization. Taxol was approved for human use by the US FDA in 1992. The US FDA and the European Medicines Agency (EMA) have approved the use of Taxol for the treatment of breast, ovarian, and lung cancer, as well as Kaposi's sarcoma. Taxol, however, was not protected by a patent. BMS was granted five-year exclusivity under the Hatch-Waksman Act.

BMS : Bristol Myers Squibb

採　点	

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3

Phlorizin was isolated from the bark of an apple tree in 1835. Its various activities, including glycosuria, were known as early as 1886. The compound's effects on lowering blood glucose levels, prevention of the reabsorption of glucose, and increased levels of glucose in urine were reported as early as 1933 from a study in a small number of people. However, the transporter effect was not limited to just the kidney, the target organism. The molecule inhibited glucose absorption in the intestines and other body organisms, thereby limiting its use. In 1995, it was discovered that phlorizin inhibited sodium-glucose cotransporters SGLT1 and SGLT2. SGLT1 is expressed in most tissues including the intestines, whereas SGLT2 is predominantly expressed in the kidneys. The inhibition of SGLT1 expressed in the intestines and other tissues caused the unwanted effect. Hence the quest to modify phlorizin began to discover and develop SGLT2-selective inhibitors by eliminating SGLT1 activity. This effort led to the discovery and development of a series of highly successful FDA-approved (2013–2023) antidiabetic agents [e.g., canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, bexagliflozin] to help control blood glucose levels in adults with type-2 diabetes.

3文とも *J. Nat. Prod.* 2024, **87**, 1235–1245 より抜粋

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