A first University existed between the 12th century and the late 15th century in Billom, with up to 2,000 students, equal to the great universities of Montpellier, Toulouse and Paris. In the early 16th century, the bishop of Clermont, Thomas Duprat, founded a university in Issoire, inaugurated by the king in February 1519. Following petitions by Charles de Bourbon and the University of Paris, however, the university was closed in 1520. In 1681, the king authorised the creation of a college of medicine in Clermont. A Faculty of Literature was created in 1808 but was closed with the Restoration in September 1815.

1854 marked the beginning of State-recognised university activity in Clermont-Ferrand. In 1872, Emile Alluard, a professor of physics, obtained the construction of the meteorological observatory on the summit of the Puy-de-Dôme, at that time the first mountain resort in Europe. The limnological station in Besse-en-Chandesse was created in 1899, with the aim of studying the fauna and flora of the Auvergne lakes. The Institute of Chemistry and Industrial Technology, which would later become the Graduate School for Chemistry, opened its doors in 1911.

It was the Second World War, however, that deeply ingrained university life in Clermont, with the transfer of the faculties of Strasbourg in 1939, fleeing German occupation. On 25 November 1943, the buildings were surrounded by the Gestapo, and the order given to arrest the deans, all foreign students and those originally from Alsace-Lorraine with potential links to the Resistance. Almost 50 students and teachers were arrested and Paul Collomp, a professor of Greek at Strasbourg, was assassinated.

The University started to take its current form in the 1970s with the building of the scientific and technical campus of Les Cézeaux and the creation of the Montluçon University Institute of Technology.

In 1976, the University of Clermont-Ferrand was divided into two entities: Clermont 1 (Legal, Economic and Medical Sciences) and Clermont 2 (Literature, Science and Technology).