The proposed Deep Underground Science and Engineering Laboratory (DUSEL) program represents a unique opportunity for collaborative interdisciplinary examination of the deep biosphere, hydraulic and fluid cycling, water-rock interactions, energy flux in the deep sequestered subsurface, evolution and genomics, and search for novel microbial traits for biotechnological exploitation. Appropriate tools have recently been developed for 3-D geophysical characterization of subsurface sampling sites, geophysical characterization while drilling, sample retrieval, sample processing, evaluation of contamination, QA/QC, sample interrogation and archiving or archival storage. Combined with recent advances in molecular biological characterization including genomics, sequencing, microarrays, and proteomics, biogeoscientists are well prepared for a time- and cost-effective investigation of Earth's final frontier. Multidisciplinary experimental programs could include examination of: deep biogeochemistry; limits of life, survival and adaptation; evolutionary gradients; eco-genomics; primitive or ancestral life; fluid, energy and organismal transport; ore and vein forming processes; and large (cubic km scale) perturbation experiments. The availability of one or more dedicated, controlled-access, isolated, subsurface environments hundreds to thousands of meters below land surface will facilitate characterizing subsurface processes and biota at scales of microns to kilometers, thereby facilitating a more comprehensive understanding of coupled biogeo-hydro-chemical processing in this and other planetary bodies.