Consumption of crude oil derived hydrocarbons is growing due to an increase in the general standard of living of the global population. Power generation and transportation sectors are the primary two sources of fuel consumption, which have raised the demand for crude oil and led to serious environmental problems. This demand forced Environmental Protection Agencies to strengthen the allowable exhaust limits. Recently, carbon monoxide, particulate matter, and NOx emission limits increased to the extent that engines must operate at higher energy densities. It is getting extremely difficult to pursue reciprocating engine efficiency research because of the limitations of fuel properties, ignition strategies, and combustion stability. Because of that reason, the Department of Energy in the United States proposed the Co-Optimization project, where fuel and combustion concepts are developed simultaneously to optimize engine operation at higher loads. Toward this goal, this doctoral study focused on the two aspects of Co-optimization program, testing new biofuel and investigating innovative engine strategy that delivers higher engine efficiencies. First, natural gas lean combustion mode was assessed by using spark ignition (SI), single-point laser ignition (2P-LI) and prechamber equipped laser ignition (PCLI) to provide higher brake power while maintaining the exhaust limits. A rigorous combustion data analysis was performed and the main reasons leading to improved performance in the case of 2P-LI and PCLI were identified. In the second part of this dissertation, a spherical bomb was designed and validated to measure the laminar burning velocity (LBV) of a promising biofuel (2,4-Dimethyl-3-pentanone (DIPK)) for homogenous charge compression ignition engines. A high-speed schlieren imaging technique was employed to ensure that the flame is stable. LBV measurements carried out at several initial conditions by diluting the mixture with N2, Ar, He, and CO2 to provide several validation points for chemical kinetic mechanism.