Enamel is the outermost covering of mammalian teeth that rarely undergoes catastrophic failure or spallation, despite a lifetime of repeated loading, in a wet-, acidic-, bacteria laden-environment. Enamel forms through a process typical of biomineralization in which specialized cells, ameloblasts, fabricate an organic extracellular protein matrix. The mixture of enamel matrix proteins undergoes self-assembly to form an enamel extracellular organic matrix that serves to control the initiation, rate of growth and habit of the inorganic crystallites. The inorganic crystallites almost entirely replace the organic phase during maturation. Thus, despite an embryonic origin in protein, mature enamel is a stiff-, brittle-, composite-ceramic composed of substituted hydroxyapatite (Hap) crystallites embedded within a small amount of organic material distributed between and/or among the crystallites. The selection of expressed genes, their timing during development and their relative abundance is under genetic control and is responsible for both the hierarchical organization of enamel and its unique physical properties. We have investigated each of these parameters in vitro and in vivo. I will describe our efforts to redesign enamel formation by changing the genes involved in matrix formation. Here, we reduced the protein complexity one order of magnitude but altered the material property of the enamel only modestly, suggesting that a biomimetic-designed material could be expected to function satisfactorily.