Next-generation sequencing, genomics technologies, and biological network reconstruction and integration are enabling systems-level understandings of organisms. At the same time, new plant transgenic methods are continuing to be developed that enable more precise manipulation of individual genes, as well as the ability to introduce a large number of transgenes. By revealing various types of molecular interactions that underlie interrelated traits such as higher wood yield, altered biomass composition, and resilience to biotic and abiotic stress, networks have the potential to accurately identify targets for manipulating multiple or single traits. However, plant networks are highly complex, and their accuracy depends on the underlying experimental plant biology. To what extent are networks identified in one plant species translatable to another species? How many different genotypes, environmental conditions, tissues, time points and developmental stages need to be studied to accurately predict targets? Do many genes need to be manipulated in order to alter complex traits? Although there are not single, straightforward answers to these questions, I will use specific examples to discuss some of the important issues.