Cannabis Genome Uncloaked: Commentary on the Scientific Implications

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In August 2011, Medical Genomics and Nimbus Informatics reported and published online the complete 400 million base-pair genomic sequence of *Cannabis sativa* (commonly labeled by the obsolete pejorative term, marijuana, in the USA): http://csativa.elasticbeanstalk.com/

This event yielded considerable uproar on newswires and Internet alike, sparking a considerable amount of speculation as to potential implications and opportunities. The human genome has been published for a decade, and has generated an impressive body of work in the mean time that may lead to a better understanding of human diseases and their treatment. What then, are the implications of this new discovery?

Firstly, while this development will, without doubt, spur further investigation, a tremendous amount of genetic work on cannabis has been accomplished previously. While Δ^9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, was characterized biochemically, and synthesized in 1964 (Gaoni *et al.*, 1964), it was not until 2004 that its biosynthetic enzyme, tetrahydrocannabinolic acid synthase (THCA synthase) was cloned (Sirikantaramas *et al.*, 2004), and crystallized the following year (Shoyama *et al.*, 2005) Its counterpart in production of cannabidiol (CBD), cannabidiolic acid synthase, was previously purified and sequenced (Taura *et al.*, 1996). See (Russo, 2011) for a recent review of the biosynthetic pathways in cannabis. This antecedent work allowed the subsequent isolation of THCA synthase from an ancient cannabis sample from Xinjiang, and even the identification of a unique single nucleotide polymorphism (SNP) (Russo *et al.*, 2008).

Thus, arguably, the genes for the most pharmacologically versatile pharmacological components in cannabis have already been identified. Additionally, the production of cannabis chemotypes ("strains") expressing high titers of specific phytocannabinoids has advanced greatly employing solely advanced Mendelian techniques. Thus, not only high-THC and high-CBD lines have been isolated for pharmacological production (de Meijer, 2004; de Meijer *et al.*, 2003), but also high-cannabigerol (CBG) (de Meijer *et al.*, 2005) and cannabichromene (CBC) plants have been developed (de Meijer *et al.*, 2009a). Additionally, plants predominating in the production the propyl-phytocannabinoid analogues, tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), cannabigerivarin (CBGV) and cannabichromivarin (CBCV) (de Meijer, 2004) have been selectively bred and are the subjects of current pharmacological research that portend to lead to interesting new pharmaceutical applications (Russo, 2011).

While the publication of the cannabis genome might simplify production of THC-knockout plants, which theoretically could be attractive for industrial hemp production, the need for such an approach has been obviated by a previous generation of plant breeding work which has allowed the development of cultivars easily meeting the

standard international requirement that such plants express 0.1% or less THC content (McPartland *et al.*, 2000; Small *et al.*, 2003; Wirtshafter, 1997). Additionally, cannabinoid-free plants have already been produced conventionally (de Meijer *et al.*, 2009b). Thus, one might reasonably question the strategy to genetically engineer cannabis when the plant itself displays incredible plasticity to produce such bountiful biochemical diversity. It is certain that the production of genetically modified organism (GMO) cannabis plants would provoke tremendous controversy among consumers, and that battles over patents and breeding rights would be obvious sequelae of such a development. Any individual or corporation anticipating dipping their toes into such an endeavor may expect to encounter a veritable regulatory minefield while attempting to license such a product.

Other nightmare scenarios are easy to imagine. One would be exemplified by the widespread Internet hoax of the 1990's that purported that a mythical Professor Nanofsky of Florida allegedly transfected THC production genes into orange seeds. While such technology might be feasible, it would likely represent no more than a laboratory carnival act in light of the cannabis plant's already prodigious production capabilities. A stealthy peppermint chemovar sporting illicit phytocannabinoids in its glandular trichomes might be a more logical choice in such underground subversive daydreams.

At present, the published Medical Genomics/Nimbus informatics cannabis sequence is not annotated, and it will require a great deal of foreknowledge and detective work for anyone to ferret out the more interesting bits of information. The real potential of this work, however, would seem to lie in the realm of epigenetics, the hereditable changes in gene expression or phenotype of the cannabis plant. For example, we currently know relatively little concerning factors regulating cannabinoid production in the plant. Similarly, the biosynthetic pathways and regulation of cannabis terpenoids remain potential research areas ripe for picking (Russo, 2011).

In summary, the publication of the cannabis genome is a welcome scientific development, but one whose potential applications remain to be determined. The possibilities are enticing, and it seems certain that many able minds will apply their imagination to the task.

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