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Editorial

On Alfalfa Bioengineering of Humans, Plants and Animals: The Tool and the Target

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This editorial seeks to succinctly and meticulously provide practical and inventive information on alfalfa's biotechnological and bioengineering capacities in improving humans, plants and animal's efficiency and health. Alfalfa (*Medicago Sativa L.*) or Lucerne, a perennial herbaceous, is the most extensively planted crop and major forage fed as hay, silage and pasture to livestock worldwide. Alfalfa has a large dry biomass yield, quality nutrient profile and a vast capability to fix nitrogen and enrich soils. With high regeneration ability, the fodder alfalfa is suitable for genetic modification via modern approaches [1,2]. Agrobacterium-mediated gene transfer has been utilized for transformation of embryogenic alfalfa genotypes [3-5]. In 1986 tobacco and sunflower calluses were first used to express recombinant human growth hormone. Thus far, diverse plant systems have been utilized to produce pharmaceuticals [1,6]. Biotechnological advances have furthered pharmaceuticals benefits of alfalfa. Expression cassettes are being optimized for protein expression in alfalfa leaves. In addition, innovative methods have been developed and renovated to express transient proteins. For instance, it is feasible to use agro-infiltration or protoplasts transformation for early demonstration and validation. Moreover, alfalfa has an exceptional ability to produce recombinant glycoproteins with uniform and homogenous glycosylation patterns. Alfalfa bioengineering represents a cost-effective and reasonably safe method for antibody production [7].

With recombinant protein expression levels of 0.1% to 1% of soluble proteins, annual recombinant protein yield of a 10-ha greenhouse could reach about 26-260 kg. Plant biopharming has greatly succeeded in producing many bioactive pharmaceuticals, including diagnostic monoclonal antibodies and blood components [8]. From an immunomedical perspective, genetically modified alfalfa is suitable for edible vaccines production [9]. Transgenic alfalfa has been utilized to express the structural protein VP1 of Foot-and-Mouth Disease Virus (FMDV) potentially for ruminants. As a bioreactor, transgenic alfalfa can produce commercial enzymes, in a process that is much cheaper than fermentation facilities construction [10]. Lactoferrin (Lf), as an iron-binding glycoprotein in human colostral whey proteins and active against many pathogens, may be generated through expression systems for recombinant Lf in transgenic alfalfa [11]. Alfalfa has an enormous capacity to generate recombinant glycoproteins with homogenous glycosylation. A gene system based on Agrobacterium tumefaciens has been used to transform alfalfa with a binary vector to carry human Lf cDNA [5]. Likewise, non-embryogenic alfalfa varieties have been applied to produce recombinant human Lf from cell cultures using Agrobacterium tumefaciens-based gene transfer. Future research will enable development of growing transgenic suspension cultures [5].

Transgenic spinach expressing epitopes of rabies virus Glycoprotein (G protein) and Nucleoprotein (N protein) may be fused to Alfalfa Mosaic Virus (AlMV) coat protein. This can be orally administered to human to trigger specific antibody responses. Potential exists for alfalfa-generated rabies vaccine to complement oral vaccinations [12,13].

N-linked glycans in alfalfa can be processed into several mature oligosaccharides with core-xylose and core-α(1,3)-fucose and terminal Lewisa epitopes. The C5-1 monoclonal antibody expression in alfalfa can produce plant-derived IgG1 that is N-glycosylated by a prime glycan with a α(1,3)-fucose and a β(1,2)-xylose attached to a GlcNAc2Man3GlcNAc2 core. Since the core is widespread in plant and mammal N-linked glycans, alfalfa plants possess capacities to produce recombinant IgG1 with an N-glycosylation. This fits well for in vitro and in vivo glycan refinement into human suited plantibodies. In vitro galactosylation of the alfalfa-derived C5-1 mAb creates a homogenous plantibody with terminal β(1,4)-galactoses similar to mammalian IgGs [14]. Leukotoxin (Lkt) has been expressed in alfalfa and administered as edible vaccines to attenuate stress and help prevent diseases in animals [2,15]. Eating foods produced from such plant-empowered animals can provide similar health benefits to humans as do original plants. Novel promoters for high-level protein expression are being developed in alfalfa leaves using alfalfa cell-culture and transient-expression technologies.

Amongst the top alfalfa's advantages are high biomass yield, nitrogen fixing, soil nutrient enrichment, and homogeneous glycan structures of the glycoproteins synthesized in alfalfa leaves. These offer reasonable economics on farm and high batch-to-batch consistency in vitro. Alfalfa leaves contain much oxalic acid that could interfere with optimal biofarming processing. For its multitude of bioactive substances, alfalfa will host nutrigeno proteo-metabolomic tools to specify its biopharmaceutical health-promoting effects. Genetic engineering will help produce biopharmaceuticals most favorable to human and animal health.

All in all, future is glorifying. Alfalfa is an inexpensive platform for monoclonal antibodies being used as potential human therapeutics and diagnostics. Plant expression systems to produce human and animal vaccines possess exclusive economical and biotechnological. However, the main concerns include biosafety, dosage uniformity, regulatory guidelines, and possible survival of herbicides and

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pesticides. Alfalfa as an ever-leading high-biotech plant will host and generate irreplaceable animal-agricultural, medical, medicinal, immunological, and omical tools to help improve humans, animals and plants efficiency and health. Alfalfa serves as both the tool and the target to immunize and optimize biosystems in animal, plant and human ecologies. Research should flourish to realize such benefits in highest capacities.

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