

New Molecular Targets for Herbicide Discovery

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Current herbicide use is dominated by active ingredients with only a few modes-of-action, including PS II inhibitors, ALS inhibitors, an EPSP synthase inhibitor and auxins (1). New herbicide target sites are needed to control weeds resistant to existing herbicides, protect the usefulness of existing herbicides, enhance efficiency and add value. Of the more than 280 registered herbicidal active ingredients, only 19 modes-of-action are known. Among the 19, only 12 have been characterized at the molecular level (Table) (2).

New target site discovery can be approached fundamentally by two means, chemical probes or genomics (Figure 1). In the former, natural products or organic chemicals are screened against whole plants and active lead compounds pursued for target site identification. The organic chemicals may be derived from traditional linear synthesis or combinatorial chemistry, in which pools of compounds are prepared around a common scaffold. A number of new tools are available to help with the screening process, including high-throughput automation technologies for sample and data handling. Molecular genetics is increasing the approach to target site identification. Resistant plants can be obtained directly by screening. Alternatively, the expression level of specific enzymes can be increased which also leads to resistance. In both cases the resistance can be traced to the genetic level and the target site identified. Other new genetic approaches for mode-of-action determination include the use of microarrays to match the mRNA response of treated plants to a database of known responses, or matching the small molecule profile of treated plants to a known metabolite library. These techniques are useful for distinguishing new modes-of-action from known, and for initial direction in new target site discovery.

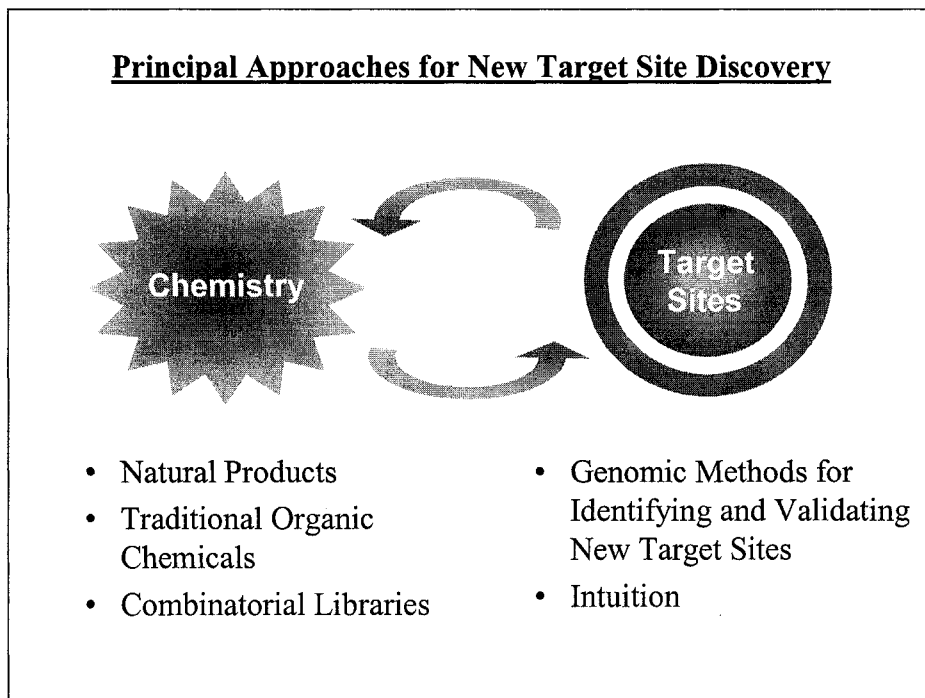
An alternative approach to target site discovery is genomics. Plants are known to have ~30,000 genes and each gene encodes a specific protein. Only a few of these proteins will be effective as herbicide target sites and these can be identified by molecular techniques, such as decreasing the expression level of a specific gene and noting the response. If slight decreases in the level of a specific protein cause significant effects on plant growth, the protein may represent a good herbicide target. Finding an inhibitor for this target site that can function as an actual herbicide may require high-throughput *in vitro* screening, molecular design technologies, or both.

New target site discovery is increasingly the focus of herbicide discovery research groups around the world. Whether the research starts with a chemical probe or the genome, molecular biology is providing the tools for identification. Despite the wealth of new technologies available in genomics, automation, and molecular design, the success of the discovery effort ultimately hinges on the initiative and curiosity of the discovery scientist.

Known Molecular Target Sites of Commercial Herbicides

Commercial Herbicide Example	Molecular Target Site
diuron	Photosystem II
diclosulam	Acetolactate synthase
oxyfluorfen	Protoporphyrinogen oxidase
haloxyfop	Acetyl CoA carboxylase
trifluralin	Tubulin
fluridone	Phytoene desaturase
sulcotrione	Hydroxyphenylpyruvate dioxygenase
glyphosate	Enolpyruvateshikimate phosphate synthase
asulam	Dihydropteroate synthetase
glufosinate	Glutamine synthetase
amitrole	Lycopene cyclase
cinmethylin	Asparagine synthetase

Figure 1: Complementary Approaches to Target Site Discovery



References:

1. D. Cole, K. Pallett, and M. Rodgers, *Pesticide Outlook*. 11(6), 223-229 (2000).
2. M. Weimer and B. C. Gerwick. *Herbicides: Identification of Biologically Active Materials*. *Encyclopedia of AgroChemicals* [in press].