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Biotechnology and chemical weapons control*

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Abstract: Biotechnology is revolutionizing the way new drugs are discovered, from a substantially empirical art to a rational, predictive process in which targets of drugs are selected on the basis of known physiology, then ligands that can bind to these targets are designed. The same process could be used to identify promising new chemical weapons (CW) agents, which would be synthesized from unscheduled precursors. Biotechnology thus has the potential of fueling CW proliferation. It can also aid the development of novel nonlethal chemical agents, the development of which could have a number of negative consequences for CW control.

INTRODUCTION

The biomedical sciences are in the midst of a revolution that began in the 1970s with the discovery of methods of recombinant DNA technology, and is accelerating rapidly with the development of genomics, proteomics, bioinformatics, and a host of related technologies. This has important implications for chemical arms control.

This revolution is changing the way new drugs are discovered. Traditionally, drug discovery has been a largely empirical art, based on the screening of natural materials for pharmacological activity, followed by fractionation, identification of the active compound, chemical alteration to improve activity, and elucidation of the mechanism of action. Knowledge of the chemical groups responsible for activity, and of the biochemical mechanisms of action, frequently allowed a rational or semirational approach to the identification of other drug candidates, or derivatives with improved activity. Nevertheless, the process has remained stubbornly empirical at its core since the discovery of penicillin in 1928.

The new technologies, and the detailed physiological understanding of health and disease that they are engendering, is fostering the development of an increasingly rational approach. Fully rational drug design is still elusive, but it is now clear that it is only a matter of time. In such a scheme, potential drug targets would be identified first on the basis of known physiology, ligands that bind to these targets would then be designed on the basis of their structural similarity to the natural ligands, or by computer modeling of their target binding sites. Ligands would then be synthesized, and their pharmacological activity determined. Already, the pharmaceutical industry is devoting a great deal of time and resources to such processes, even though empirical methods still are a component of most drug discoveries.

These new approaches are driven as much by advances in instrumentation and control as they are by new knowledge—for example, high-speed DNA sequencers, microrobotic machines that produce and read microarrays, that perform the reactions of combinatorial chemistry, and that conduct auto-

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mated high-throughput screens, as well as the software that controls these machines and that compares and analyzes the data that they produce.

Of course, discovery of CW agents shares much with the discovery of new drugs; only the intent and desired outcomes differ. Thus, the biomedical revolution, which promises a vast array of new drugs, also has its dark side; the same techniques could be abused by states desiring to develop a new generation of chemical weapons [1]. This promises to seriously complicate CW control, unless States Parties are willing and able to adapt the enforcement of the Chemical Weapons Convention (CWC) to the changing technology.

BIOCHEMICAL TECHNOLOGY

Among the many new technologies that underlie the biotechnological revolution are some with particular relevance to the discovery of new chemical weapons. These technologies are evolving with great rapidity, due to the immense benefits and profits that they promise, via the development of new diagnostic and therapeutic agents. However, the detailed understanding of the physiology of health and disease that will accrue from this will simultaneously lay the basis for the development of new CW agents, both lethal and nonlethal. Biotechnology is also very rapidly disseminating around the world, and it will not be long before the technical infrastructure to support an advanced biochemical weapons development program will be widely distributed.

Genomics is at the core of the new technology [2]. The term refers to the determination and use of whole-genome DNA sequence information, and it rests on the rapidly expanding capability of automated, high-throughput sequencers. The availability of the sequence of the human genome makes it possible in principle to recognize all proteins of a given class from their sequence (for instance, different representatives of a particular type of neuroreceptor). Genomics thus greatly facilitates the recognition of promising drug or CW agent targets.

DNA microarray technology [2] is a way of analyzing the **transcriptome**—the set of mRNA molecules that determines the instantaneous rate of synthesis of each different protein. Based on genomic sequences, glass slides or silica chips are impregnated with thousands of tiny dots, each containing millions of copies of single-stranded DNA with a sequence specific to one gene in the genome. Such chips can have one or more spots specific for each gene in the genome. The chips are then flooded with a solution of mRNA (or a DNA copy thereof) from a cell; the RNA has been made fluorescent, so that when it binds to the DNA on the slide, the spots become fluorescent and the amount of fluorescence indicates the rate at which the gene was being expressed. Such techniques are helpful in identifying the function of unknown genes, as the pattern of expression in different cells, or in cells under different conditions can suggest a function. Microarrays can identify differences in gene expression in different cells, and can thus help in identifying particular targets for drugs or CW agents.

Microarray technology is also used in **toxicogenomics** [3], in which genomic information and microarrays are used to predict the toxicity of chemical compounds. The changes in patterns of gene expression that result from the exposure to toxic compounds can be quite distinctive, and thus the response of a cell exposed to a new compound, as measured by microarrays, can give a good indication whether it will be toxic. This is important to the pharmaceutical industry in order to avoid going into clinical trials with a compound that will turn out to be too toxic to develop for a drug; it is obviously also relevant to the CW designer.

Proteomics [4,5] is the study of the entire complement of proteins of the cell. This is to some extent approachable through microarrays that measure transcription rates; but so much of the activity of the proteome is controlled through posttranslational modifications, or protein–protein interactions, that direct study is necessary. Much of proteomics is currently devoted to protein separation and the mass-spectral analysis of their fragmentation products, to allow them to be matched to gene sequences in the genome. Protein chips, in which each spot contains millions of molecules of a particular protein, are under construction, and a proteome chip for humans will eventually result. Such chips will allow the

determination of interactions among proteins, and will allow probing of the entire proteome for ligand binding.

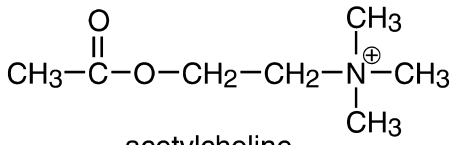
Furthermore, it is becoming feasible to predict protein three-dimensional structure from the genomic DNA sequence [6]. Thus, the long term may see entirely virtual drug design, with targets recognized in genomic sequences, their three-dimensional structure predicted by computer programs, their active site modeled, and ligands designed that will bind tightly in the active site. Only the actual testing of ligands as drug candidates would use real compounds.

Combinatorial chemistry [7] allows the rapid synthesis of a range of structural variants of a compound. It is performed in microscale computer-controlled reactors, in which sequences of reactions generate so-called "libraries" of hundreds or thousands of related compounds. These can then be tested for biological activity against purified proteins, cells, etc. in high-throughput screening systems, also robotically controlled [8]. Such techniques are already in extensive use in the pharmaceutical industry, and it is estimated that in the aggregate more than 3 million new compounds are synthesized and screened per year.

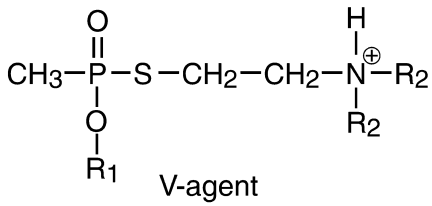
Computer technology is central to all of this. The microrobotics that much of the technology relies on are computer controlled, and they generate massive amounts of data that is stored and analyzed digitally. The management and analysis of these large biological databases is termed **bioinformatics** [9].

IMPLICATIONS FOR NEW CHEMICAL WEAPONS DEVELOPMENT

A country wishing to develop a covert CW capability would be able to use biotechnology to develop novel weapons, or variants of existing weapons. As an example, consider how nerve agents might be developed today had they not already been discovered. Consideration of potential targets for CW would naturally include the neuromuscular synapses that control such vital functions as respiration, and acetylcholinesterase would quickly be identified as one of several key proteins for which inhibitors might be highly lethal. Using combinatorial chemistry, thousands of structural analogs of the natural ligand for the enzyme, acetylcholine, would be made and tested against purified acetylcholinesterase. Those that bound tightly would be tested for lethal activity in animals. It is highly likely the V-agents (Fig. 1)



acetylcholine



V-agent

Fig. 1 Top: acetylcholine, a neurotransmitter whose accumulation in the neuromuscular synapse is transient due to hydrolysis by acetylcholinesterase. Bottom: the V-agents, structural analogs of acetylcholine; R_1 and R_2 are alkyl groups (commonly ethyl, isopropyl, or butyl). The amine is shown protonated, the form that would be found in solution in the neuromuscular synapse.

would emerge from such an approach, and quite possible that even more lethal agents than the ones currently stockpiled would be identified.

Thus, by these means, it should be feasible to identify a number of promising candidates for new chemical weapons, made from unscheduled precursors. Such a CW program could remain completely invisible to the current verification regime. This suggests that it will be important for the Technical Secretariat or the Scientific Advisory Board to continually monitor a wide range of medical biotechnology publications to remain current with trends in molecular pharmacology, alert to the potential for abuse of some of this information. It will also be necessary for the Conference of States Parties, or Review Conferences, to be willing to amend the schedules of chemicals if novel compounds emerge that constitute serious CW threats.

NONLETHAL WEAPONS PROBLEM

Nonlethal chemical weapons (NLCW) are clearly covered by the CWC, which defines a CW agent as "any chemical, which through its chemical action on life processes can cause death, temporary incapacitation, or permanent harm to humans or animals…" However, the CWC also has an exclusion that exempts from prohibition chemicals that are intended for "law enforcement including domestic riot control purposes." Thus, nonlethal chemical compounds intended for use as riot-control agents (RCAs), and munitions to deliver them, are legal for domestic riot control under the CWC. However, "Each State Party undertakes not to use riot control agents as a method of warfare."

At least one State Party (the United States) interprets the phrase "method of warfare" as implying international conflict, and thus concludes that RCAs may be used in other forms of armed conflict (often termed "military operations other than war"), such as counterterrorism, hostage rescue, embassy protection, etc. This has led this State Party, and probably others as well, to embark on a project to develop new NLCW, and military-style munitions to deliver them. However, even if this very narrow reading of the phrase "method of warfare" is accepted, it is still far from clear that the U.S. program is legal under the CWC, as its law enforcement purpose is unclear [10].

Beyond its dubious legality, the development and eventual deployment of NLCW is a serious threat to the CWC for many substantive reasons:

- it would provide a rationale for the development, production, and stockpiling of military chemical munitions and other delivery devices, and for training troops to use them (making a mockery of the Article 1c prohibition of "military preparations to use chemical weapons");
- it would provide a nearly impenetrable cover for lethal CW development, production, and stockpiling;
- synergistic pairs of NLCW may have lethal effects (and the technologies described above can help to discover such pairs);
- it would provide militaries of the world with capabilities that can readily be abused—for instance, to modify human cognition, emotion, volition, perception, arousal, bodily control, etc;
- it would enhance government ability to control civil disturbance—a capability of much greater utility to dictatorships than democracies;
- it seriously erodes the norm against chemical weapons, and the norm against targeting noncombatants; and
- it would lead to countries entering wars with an arsenal of weapons whose use is prohibited—precisely the situation that the CWC is designed to prevent.

For these reasons, it is important for the Review Conference to address the problem of NLCW. Ideally, countries that are pursuing such weapons would be persuaded that the threat they pose to the arms control regime outweighs their military utility. If States Parties can agree on this, then the Review Conference could agree that "method of warfare" is much broader than international conflict.

To strengthen measures against the use of RCAs as chemical weapons, it would also be useful for the Review Conference to convene a panel of experts to recommend munitions acceptable for use in permitted law-enforcement activities (such as hand- and rifle-propelled grenades), and ones that are not acceptable (perhaps artillery and mortar shells, missile warheads, aerial bombs, aerial sprayers). Such an understanding would limit the ability of States Parties to use RCAs as a method of warfare, and would prevent them from entering conflicts with a stockpile of munitions whose use is prohibited.

Unfortunately, consensus on the above measures is unlikely, and it is probable that there will be significant proliferation of NLCW in the near future. Thus, this issue promises to present an enduring problem for the Convention. Indeed, in the medium and long term, it promises to be the single most serious threat to the continued viability of the CWC.

CONCLUSION

Biotechnology is one of the most rapidly developing fields of human endeavor, and it promises to be the defining technology of the 21st century. It has the potential for great medical and other benefits to humanity, but its dark side includes the capability for military weapons that may ultimately become comparable to nuclear weapons as threats to humanity [11]. The most immediate threat is its application to the discovery of novel CW, especially NLCW. This could, in the long term, fatally undermine the regime against CW, and is thus a threat that deserves serious consideration by the Review Conference.

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