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The New Chemistry of Antibodies

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The promise of the use of antibodies in medicine dates back almost 100 years to Erlich's side chain theory and its subsequent incorporation into his concept of the Zauberkugel ["magic bullet" (Royal Institute of Public Health, London: Lewis, 1908)]. Only now, after a century, is the huge therapeutic potential of antibodies being realized outside of the realm of vaccination programs.

Today antibodies play a major role in chemistry and medicine with at least 17 different antibodies approved for therapeutic use and hundreds more in clinical trials. These human monoclonal antibodies are the essential embodiment of the "passive immunization" strategies introduced to aid patients who could not or should not be immunized. They can now be treated with antibodies "raised" outside of their body and endowed with affinities, and selectivity that the patient's immune system might not be able to produce. In addition these antibodies can be conjugated to toxins to destroy target cells.

There are several main reasons for the recent broad front scientific and medical breakthrough in use of therapeutic antibodies:

1. There is an ever increasing list of target antigens due to our improved understanding of the role played by certain proteins in health and in disease or as specific markers on cancer cells.

2. The realization that antibodies, themselves, are capable of carrying out chemistry of a complexity far beyond that of simple binding. This includes catalytic reactions and covalent binding to antigens.

3. Advent of combinatorial antibody libraries that allow access to the entire diversity of the immune system such that one can harvest any antibody no matter how rare. Indeed, one can access any antibody that an individual has ever made irrespective of whether it is currently being produced. We have termed this the "fossil record" of an individual's immunological history.

4 The classical Kohler-Milstein way of producing monoclonal antibodies has been enhanced and supplanted by the use of combinatorial libraries that contain many more antibodies to each antigen permitting selection of antibodies with higher selectivity and avidity than the hybridomas. Furthermore the long process of "humanizing" mouse monoclonal antibodies to avoid immune response to them in humans can be

avoided when the antibodies are selected from human combinatorial antibody libraries such as is now routinely done. Antibodies to such toxic substances that would kill the organism or the hybridoma are now routinely selected and used as toxin antidotes where none existed before.

Perhaps most importantly the combinatorial library allows production of antibodies without immunization.

5. The ability to combine these methods to select/create antibodies that do not exist in nature either because the natural repertoire is limited and/or the phenomenon of immune tolerance precludes the existence of antibodies to certain self-antigens. For example, the human antibody "Humira" to treat Rheumatoid Arthritis was harvested from a human combinatorial antibody library to a self antigen (TNF_) and then the heavy and light chains were shuffled to achieve improved binding.

To illustrate the new chemistry of antibodies I will discuss some of the latest advances made by use the combinatorial antibody library methods including:

1. Production of human antibodies that bind to metastatic breast cancer cells but not the parental tumor. These antibodies block the process of metastasis and kill metastatic foci that are already established.

2. Harvesting rare human antibodies where the antibody CDR's have evolved portions of the natural ligand for cell-surface receptors. In a remarkable example of "convergent evolution", it was shown that antibodies and natural ligands can evolve the same amino acid sequences. These convergent sequences are necessary for recognition and binding of the receptor by the natural protein ligand as well as the antibodies.

3. Preparation of catalytic antibodies that make covalent bonds with their antigens. In addition to offering new ways to destroy antigens such antibodies can lend long "antibody half-lives" to shorter lived drugs and peptides. In cancer therapy, covalent antibodies can give immune effector function to cell-specific molecules that are otherwise not sufficiently toxic to remove tumor cells.