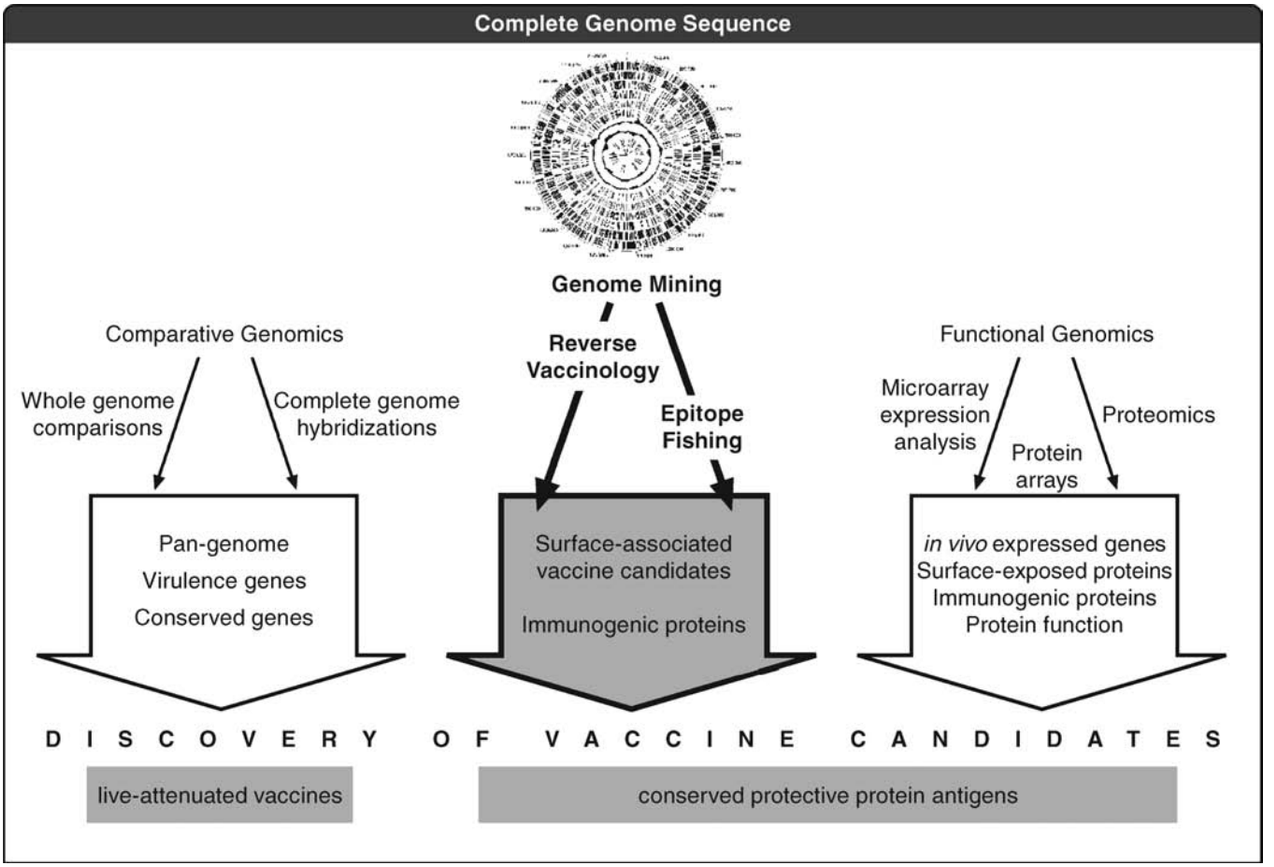

Figure 1 Developing vaccines through genomics: a new interdisciplinary realm of inquiry. The advent of genomics has revolutionized the way in which potential vaccine candidates against bacterial pathogens are identified. The genome sequences represent an inclusive virtual catalog of all the potential vaccine candidates, which may be mined to select the molecules that are likely to be effective through either ''reverse vaccinology'' or ''epitope fishing'' approaches. Genome comparisons of strains representative of genetic diversity can be a powerful tool for selection of broadly protective combinations of proteins as well as the identification of virulence factors, which may be exploited for attenuation. Functional genomics approaches are complementary to in silico antigen discovery and can contribute important information on in vivo expression, localization, and immunogenicity of antigens of an organism as well as functional roles of these proteins.

Pioneering Work of MenB: from One Genome to Universal Vaccine

MenB is an example of where several decades of conventional vaccine development had been unsuccessful because the components identified by conventional approaches were identical to self-antigens or were hypervariable in sequence. In collaboration between Chiron Spa and The Institute of Genomic Research (TIGR) (35), the complete genome of the virulent strain MC58 was sequenced (36), and within 18 months of beginning the sequencing, more than 600 potential vaccine candidates had been predicted using computer analysis; 350 of these were expressed in *Escherichia coli*, purified and tested for their ability to elicit protective immunity (37). Antisera raised against the purified proteins were assayed for specificity (by Western blot), accessibility on the surface of the pathogen (by flow cytometry), and their ability to kill bacteria when combined in vitro with human complement (bactericidal assay). The ability to evoke bactericidal antibodies, inducing complement-mediated killing of the bacteria, correlates with an antigen's capability of conferring protection against the organism (38). This approach identified 28 novel protective antigens, several of which were conserved in a panel of strains representative of the meningococcal population and therefore likely to induce immunity against all meningococcal isolates. In essence, in under a year and a half, reverse vaccinology applied to MenB enabled the identification of more vaccine candidates than had been discovered during the previous 40 years by conventional methods. Moreover, the antigens identified using the genome-based strategy were different from those identified using conventional approaches.

To strengthen the protective activity of the single protein antigens and to increase strain coverage and to avoid escape mutants, the final vaccine formulation comprises a ''cocktail'' of the selected antigens. These promising vaccine candidates are currently being tested in clinical trials (39) and are giving promising results. Importantly, this work also shows that