ISSN No:-2456-2165

The Modern Aeon of Vaccine Development: Reverse Vaccinology

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Abstract:- As we witness the evolution of technology day by day and how it revolutionizes all the applied fields too. In this review article we will know about how advancement in technology affected the way we procure vaccines, how we found a more convenient method and how it has been used and achieved results. What led to the discovery of Reverse vaccinology? The approach it uses for determining potential vaccine candidates and tools that have been developed to ease one's research and how the approach is different from that of the conventional method.

I. INTRODUCTION

As per the Dutch philosopher, Desiderius Erasmus "prevention is better than cure" and biologically prepared immunization also known as vaccines, are the best-sought way of preventing a certain disease. It has been over two centuries since the first vaccine was developed for smallpox in 1796 by Edward Jenner and since then humanity has been able to develop vaccines for various diseases such as polio, mumps, rubella, measles, hepatitis, cholera, yellow fever, covid and many more. Due to his active immunization, we were able to eradicate one of the deadliest diseases such as polio. By this, it is ipso facto that creating immunity against pathogens is vital for the sake of humanity. There are various methods through which vaccine development has been carried out such as live attenuated vaccines, inactive vaccines, DNA vaccines, recombinant vaccines, and many more. The major drawbacks of these procedures are that they require an immense amount of time and lots of resources. Reverse vaccinology is a concept that tries to overcome these drawbacks and make procuring vaccines easier. It is a step up from the conventional methods used earlier for vaccine development which employs bioinformatics, its tools, and reverse pharmacology practices.

II. HISTORY

Rino Rappuoli currently the head of vaccine research and development at "GlaxoSmithKline" was the first to give us the basic conceptual idea of reverse vaccinology. The first vaccine was developed in the 1990s this method was against Neisseria meningitides (serogroup B meningococcus) by Rino Rappuoli along with the J. Craig Venter Institute.

Now the question every reader must be asking is, what is reverse vaccinology? And what led to its development. By 1995 the first-ever genome sequence of a living organism was published and by the end of the 20th century tons of genome sequences were available. As the technology advanced and people started getting ways to handle huge amounts of data such as the genome this called for the development of newer techniques like WGS which stands for whole-genome sequencing. WGS led a revolutionary wind in the field of reverse vaccinology, microbiology, pathology, and various other biological fields. Hence, we can say that the key factors which influenced the development of reverse vaccinology are, technology, availability of genome sequences, and whole-genome sequencing techniques.

J. Craig institute along with the other researchers continued on the path for vaccine development through reverse vaccinology and was successful in procuring vaccines for A Streptococcus, B Streptococcus, Staphylococcus aureus, Streptococcus pneumonia, and many more

III. APPROACH

The major step in reverse vaccinology is the screening of the entire genome of a specific microorganism using various bioinformatics and computational biology tools. The screening of the genome helps us to anticipate the genes present in the microorganism which might show antigenicity and code for a protein with extracellular localization, signal peptides, and B cell epitopes which then calls for the filtration of the genetic attributes to obtain the desired one. The desired gene attributes are then produced synthetically and then screened in the animal model of the infection.

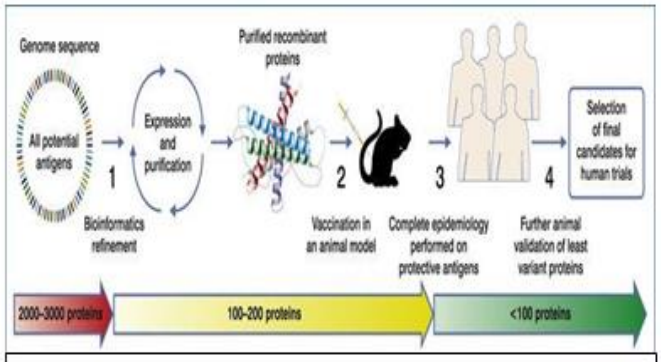

Fig.1 approachable way for procuring vaccine through reverse vaccinology

IV. ACCESSIBLE TOOLS

The practical uses of reverse vaccinology are now a common thing but still, many general laboratories don't have access to such advanced software through which they can perform this technique. Recent development in science and technology are giving us hope that someday this technology will be available in every laboratory.

There is various software available such as:

➢ *NERVE:*
- NERVE stands for "New Enhanced Reverse Vaccinology Environment"
- It is a must-download data processing program
- This saves time by combining various steps into one program
- It doesn't include all the epitope
- prediction
- User-friendly software
- Integrates multiple robust and well- renowned algorithms for the analysis and comparison of protein.

➢ *VAXIGN: (vaccine design)*
- It is a web-based publicly accessible software
- Developed by 2008
- Gives extremely accurate information.
- Helps in the identification of vaccine targets.
- Employs PSSMs (position-specific scoring matrices) for analyses of the protein sequence or alignment.

➢ *RANKPEP:*
- This is kind of similar to VAXIGN
- Predicts the peptide bonding in MHCI and MHCII molecules
- Helps in sequence alignments through position-specific scoring matrices (PSSMs)

V. APPLICATION OF REVERSE VACCINOLOGY:

➢ *MENINGOCOCCUS B:*

This variant causes over fifty percent of meningococcal meningitis. Meningitis B is one form of meningococcal disease that attacks the brain and spinal cord and causes selling in these areas and causes a serious infection of the bloodstream known as septicemia. Approximately 10 to 15% of people die fromthis disease.

Its unique structure makes it difficult for one to procure its vaccine. The polysaccharide shell of meningococcus is identical to that of human self-antigen but varies a lot from its surface proteins. Rappuoli and others of the J Craig institute sequenced the Men B genome and scanned for potential antigens. For the first time, they found 600+ potential antigens which were tested by expressing in E coli.

Several potential antigens were selected based on their universality and many of them proved to be successful too in mice but they couldn't effectively interact with the humane immune system and didn't induce a good immune response, this was because the proteins alone couldn't generate such powerful immune response.

Later on, via the conventional method, outer membrane-bound vesicles containing polysaccharides were added from the purification of bulks on gram-negative cultures which enhanced the immune response of humans as per requirement. (2,3)

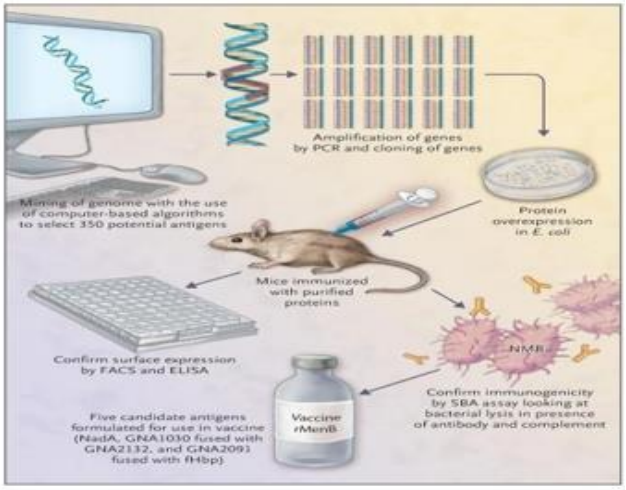

Figure 2. Men B vaccine process

➢ *TUBERCULOSIS:*

Tuberculosis is a bacterial infection caused by mycobacterium tuberculosis which is an aerobic, nonmotile bacillus with a slow division rate. TB is generally spread through the air via the aerosol particles emitted by the infected individual after a sneeze or a cough. Its symptoms include cough, night sweats, fever, weakness, fatigue, weight loss, blood coughs, etc. individuals with a weak immune system are more likely to be affected by the bacteria. The infection majorly attacks the lungs but can attack other body parts such as the brain, liver, etc.

By the 18th of July, 1921 a vaccine for tuberculosis was developed which has been widely used to date but now the issue that arose is that it is only moderately effective for the new strains of tuberculosis. Since 2006 the rise of the new strains of tuberculosis has been observed. Strains such as MDR-Tb (multi-drug resistant tuberculosis), and "extensive drug-resistant Tb" are quite difficult to treat as they are resistant to very powerful anti-tuberculosis drugs.

Reverse vaccinology is a method that is being used to develop a novel potential vaccine candidate against tuberculosis. Hence, the proteome of M. tuberculosis H37RV was analyzed through nerve which identified 331 proteins, some of which might be potential vaccine targets, they were again analyzed by VAXIGN for determining their antigenicity value resulting in the discovery of 73 antigens and finally 6 novel vaccine candidates were selected "Esxl, PE26, PE65, PE_PGRS49, PBP1, and Erp" which might be used to design or improve the M. Tuberculosis vaccines.

Pseudomonas aeruginosa Pseudomonas aeruginosa is a bacterium that is found in soil and water. These bacteria majorly cause infections post- surgery like blood, lungs, and other body parts. P. aeruginosa belongs to the multi- drug resistance (MDR) ESKAPE pathogen. These bacteria can adapt to different conditions of growth and escapes the immune recognition of the host, it also has high variability of proteins among different

P. aeruginosa strains and within the same strain too, which is why procuring its vaccine is quite complicated. With the help of bioinformatics tools, we found 52 potential antigens which were obtained from patients suffering from cystic fibrosis. These 52 potential antigens were selected from 5570 open frames of the P. aeruginosa genome by applying various filters to exclude the proteins predicted not the be present on the bacteria, surface, to be variable in different strains, to have homology to human or e coli proteins. Out of the selected 52 candidates, 30 gave successful results. (7,8)

- *SARS-CoV-2*

It has been over 2 years since the first outbreak of covid 19 in India and we are still recovering to date. WHO announced the global outbreak causing covid 19 as a pandemic by the 11th of march 2020. This outbreak created a mass panic showing us the immediate need for vaccination. Since then, people in science around the globe have developed and are still developing ways to immunize people from covid 19.

SARS-CoV-2 is a single-stranded positive- sense RNA belonging to the genus Betocoronavirus of the Coronaviridae family. Some members of this family affect humans causing humans to cause the common cold HCoV229E, HCoVNL63 and HCoVC43, SARA (severe acute respiratory syndrome), and MERS (middle east respiratory syndrome) SARS-CoV-2 encodes for structural as well as non-structural proteins. Structural protein includes spike protein (S), envelope protein (E) membrane protein (m), and nucleocapsid protein (n).

In the past year, various research papers were published by the journal of biomolecular structure and dynamics which were mainly based on the research of “E, M, N protein and ORF10, ORF8, ORF3a, and M protein. Using bioinformatics tool for the development of covid 19 vaccine. It has been observed that a strong t-cell response is necessary for respiratory virus infection.

That is, we need both humoral and cellular immunity to get proper protection. The idea of the multi-epitope vaccine was put forth because it could recognize and assemble B and T cell epitopes which could trigger the immune system and induce more potent immune responses and give longer protection to the individuals. (2, 6)

- *MALARIA*

Malaria is caused due to a protozoan known as plasmodium which needs two host for completion of its life cycle one is human and the other is female anopheles’ mosquito which also acts as a vector.

An enzyme called carbonic anhydrases are seen to be highly expressed in the midgut and ectoperitrophic space (Outside a semi- permeable, non-cellular structure which surrounds the food bolus in an organism's midgut). One of the possible potential vaccine candidates for the control and prevention of malaria are transmembrane carbonic anhydrases (tmCAs).

Two groups including a group α-CAs and one group of η-Cas under the tmCAs were analysed by immunoinformatic and computational biology tools.

The result obtained in the experiment revealed that as assumed tmCAs from the plasmodium species are indeed potential targets for vaccinations against malaria. (1,4,5)

VI. DEVELOPMENTS AND ONGOING RESEARCHES IN THE FIELD

Found the presence of pili in gram positive pathogen such as in A streptococcus, B streptococcus and pneumococcus. It diverted the major focus to biological study of pathogens Paved the path for discovery of G binding protein factor present in meningococcus which binds to factor H in humans which is complementary to the prior, this binding allows meningococcus to grow in human blood while blocking alternate pathways. Ongoing research on the development of a multi epitope vaccine avian pathogen mycoplasma gallisepticum Designing of a multi epitope vaccine against mycobacteroides abcessus by pangenome-reverse vaccinology (2,7,8)

VII. CONCLUSION

Reverse vaccinology is a step up from the conventional method in all senses that is time efficiency, better results as well as cost effectiveness but there is always room for improvement as now the technique only considers protein as targets, whereas the conventional method also took biomolecules such as polysaccharides into consideration. As the technology and the health sciences are developing day by day all our previous practices are going to be surpassed one day or the other which will lead to the development of the entire world and lead towards a better world, a healthy world.

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