OMICS GUIDED VACCINE DEVELOPMENT: R&D AND INDUSTRY PERSPECTIVE

Dr Ramesh Chandra Pandey
Associate Manager,
Life science and Clinical development consulting
Value Edge Research Pvt Ltd

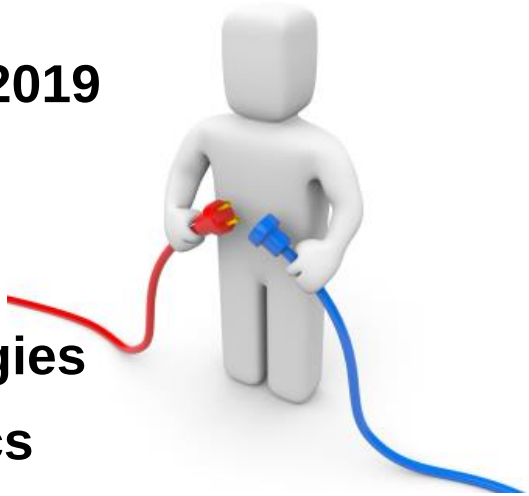
COI statement: The analysis presented is the outcome of secondary research of the author

8TH INDO GLOBAL SUMMIT & EXPO ON VACCINES, THERAPEUTICS & HEALTHCARE
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VACCINE + OMICS = VACCINOMICS

Vaccine industry:

- **Estimated industry worth > $ 56 Billion by 2019**
- **High impact on public health**



Omics:

- **Approach using high throughput technologies**
- **e.g. Genomics, Proteomics, Transcriptomics**
- **Highest level of intrusion in almost all disciplines**

Why vaccinomics:

It can help in indentifying vaccine targets for organisms with highly variant antigenic repertoire in a more systematic manner…

References: Market watch,

DESPITE SUCCESS STORIES OF VACCINE INDUSTRY, THERE ARE CHALLENGES TO TACKLE

Vaccine industry is highly dynamic (WHO)

- Developed vs Developing countries
- Innovation vs cost effectiveness
- Traditional monovalent vs multivalent vaccines

Successes : Small pox and Poliomyelitis

Challenges of 21st century (some examples)

- Pathogens with high sequence variations – e.g. Malaria, TB, HIV, HCV, TSV, Influenza, Dengue
- Efficacy and Valancy
- Affordability (cost), availability (production and supply) and accessibility (regulatory and pricing)

References: Doolan etal., 2014,

DOMINATED BY TOP 5 COMPANIES, THERE IS A SURGE IN POLYVALENT VACCINES

Companies	2014 (Billion $)	Annual growth	Lead products (only selected vaccines, not exhaustive list)
Merck	6.25†	8%▲	Gardasil (HPV), Gardasil 9 (multivalent), RotaTeq
Sanofi	5.85†	7%▲	Fluzone, Pent Act HIB
GlaxoSmithKline	5.26	6%▲	Pediarix (DTPHib Polio), Hepatitis (A&B), Vervarix
Pfizer	4.48	13%▲	Prevnar 13 (Pneumococcal 13-valent)
Novartis	1.53	10%▼	Flu, Meningitis
Total (Top 5 company)	23.37	Top 5 companies hold the >90% of the vaccine market, globally (as per 2014 data)	
Vaccine industry total revenue	25.5		

†Sanofi and Merck share 50% revenue of Gardasil 9, and overlapping vaccine portfolio

References: Fierce vaccine news, PRNewsWire,

COMPLEX GENETICS OF CANCER, HIV, MALARIA POSE CHALLENGE IN VACCINE DEVELOPMENT

Companies	2014 (Billion $)	Lead products (only selected vaccines, not exhaustive list)	Assets in clinical development (only selected assets, not exhaustive list)
Merck	6.25†	Gardasil (HPV), Gardasil 9 (multivalent), RotaTeq	Ebola, Shingles and Bulk Varicella,
Sanofi	5.85†	Fluzone, Pent Act HIB	C. Difficile, TB, Dengue
GlaxoSmithKline	5.26	Pediarix (DTPHib Polio), Hepatitis (A&B), Vervarix	Malaria, Ebola, RSV, TB, HIV
Pfizer	4.48	Prevnar 13 (Pneumococcal 13-valent), Meningitis B	Cancer vaccines, CMV, S. aureus, C. Difficile
Novartis	1.53	Flu, Meningitis	Meningitis

†Sanofi and Merck share 50% revenue of Gardasil 9, and overlapping vaccine portfolio

References: Fierce vaccine news,

MODERN ERA OF VACCINOLOGY IS MULTIDISCIPLINARY AND INFLUENCED BY GENOMICS, TRANSCRIPTOMICS AND PROTEOMICS

- The first pathogen to be completely sequenced was H influenzae (1995)
- Now, almost all pathogens have been sequenced – including Plasmodium, HIV, tuberculosis and others
- In addition to this genomic data, other high throughput data are also available w.r.t:
  - transcriptomics and proteomics technologies,
  - microarray DNA chip, mass-spectrometry,
  - yeast two-hybrid (Y2H) screening
  - RNA-seq, NSR-seq and CHIP-seq,
  - Some pathogens have also been characterized at the level of regulation, interactome, metabolome etc.

References: Fleischmann et al., 1995

IDENTIFYING SIGNALS AND TARGETS FROM COMPLEX GENETIC ARCHITECTURE BY OMICS

Omic analysis approach in identifying vaccine targets typically involves following steps:

- Whole genome sequencing
- ORF analysis – *in silico /in vitro + Biostatistics, Bioinformatics*
- ORF expression – to determine expressing peptides/antigens
- Surface expression – by ELISA and Flow cytometry
- Study of immune response to selected antigens
- Phylogenetic analysis – to determine conserved region
- Identification of appropriate antigens for vaccine development

MENINGOCOCCAL MENINGITIS : AN EXAMPLE OF SUCCESSFUL OMICS GUIDED VACCINE

Meningococcal meningitis and septicemia is caused by *Neisseria meningitis* (with 5 major pathogenic serotypes)

Scientists faced key challenges like:

- Sequence variation of surface-exposed proteins
- Cross-reactivity of the serogroup B capsular polysaccharide with human tissues

Omic guided vaccine candidate discovery (Pizza et al., 2000 Science):

- Entire genome of N meningitidis (serogroup B or MenB) was sequenced
- ~350 candidate antigens were expressed
- Following surface expression and immunogenicity studies 7-9 antigens were determined as potential vaccine antigen
- These antigens translated to become meningococcal vaccine

References: Pizza et al, 2000, Goringe and Pajon 2012

PROGRESS AND PROSPECTS IN OTHER DISEASES: MALARIA

For most of the past half century, malaria researchers attempting to develop a pre-erythrocytic stage malaria vaccine have focused almost exclusively on a single antigen, the circumsporozoite protein (CSP).

- RTS,S vaccine (Mosquirix) – a CSP based recombinant vaccine could protect ~40% of malaria-naive volunteers (GSK and Walter Reed Army Institute of Research (WRAIR, US))
- After 30 years of development, phase 3 data showed that the vaccine is far less efficacious in the target population and the effects were short-lived

Optimal efficacy and long term protection remain an challenge with malaria vaccine

Plasmodium Omics

•High throughput data for plasmodium has been made available on public domain (e.g. www.plasmodb.org)

•The next step is to analyze these massive data to identify vaccine targets and subsequent translation

References: Doolan etal., 2014,

SUMMARY

- **Despite the huge efforts, vaccine industry is facing challenges with pathogens with variable antigen repertoires/sequence variations**
  - Difficulty to achieve optimal efficacy
  - Difficulty in getting long term protection
- **One of the ways to address these challenges is to applying VACCINOMICS**
- **Omics guided vaccine design has a potential to identify vaccine candidate antigen in pathogens like Malaria, HIV, Influenza**
  - Meningococcal meningitis success story sets an example
  - Diseases like Malaria (and also TB, HIV and cancer vaccines) look forward to high throughput applications in identifying novel vaccine targets



THANK YOU FOR YOUR ATTENTION

Discussion



Future catch up



rcpandey.vs@gmail.com

ramesh.pandey@valuedge.com

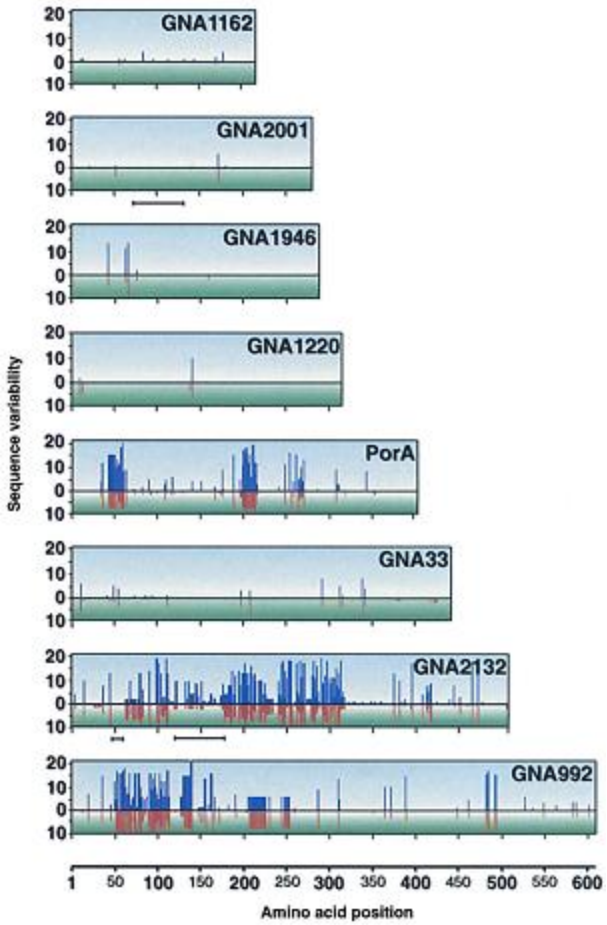


Fig. 2. Schematic representation of amino acid sequence variability within *N. meningitidis* of the seven antigens reported in Table 1 and of PorA. Abscissa, amino acid position; ordinate, number of strains analyzed. Line 0 represents sequence of the MC58 reference strain. Amino acid differences from the sequence of MC58 within the 22 strains of MenB are indicated by blue lines above the 0. Amino acid differences within the nine *N. meningitidis* strains from serogroups A, C, Y, X, Z, and W135 are indicated by red lines below the 0. Height of blue and red lines represents the number of strains with amino acid changes. Variable regions appear as blue and red peaks. Bars below GNA2001 and GNA2132 represent segments that are missing from some strains.

Table 2. Presence of genes in *Neisseria*.

Gene	*N. meningitidis*		*N. lactamica* (1 strain)	*N. cinerea* (1 strain)	*N. gonorrhoeae* (3 strains)
	B (22 strains)	A,C,Y,X,Z,W135 (9 strains)			
gna33	+	+	+	+	+
gna992	+*	+	+/−†	+/−	−
gna1162	+	+	+	+	+
gna1220	+‡	+	+/−	+/−	+
gna1946	+	+	+	+/−	+
gna2001	+	+	+	+/−	+
gna2132	+	+	+	−	+
porA	+	+	+	−	+

*In strains NG6/88 and NGF26 the start codon is 222 bases downstream from the starting codon in the other strains. †+/− indicates a negative PCR but positive Southern blotting. ‡In strain BZ133 a deletion of 31 nucleotides causes a frameshift in this gene.

Several new vaccines can be potential blockbusters in 2020

Stage	Underlying disease/ vaccine	Blockbuster potential in India
Registration	▪ H5N1 Influenza (Aflunov, KD 334, Others)	▪ Medium
	▪ Hepatitis E (Hecolin)	▪ Low
Phase 3	▪ Dengue	▪ High
	▪ Pseudonomas	▪ Low
	▪ Malaria	▪ High
	▪ Enterovirus 71	▪ Low
Phase 2	▪ Hepatitis C	▪ Low
Phase 1	▪ Difficile	▪ Medium
Pre-clinical	▪ Chikungunya	▪ High

SOURCE: TrialTrove; Press search

McKinsey&Company