



Promising *Acinetobacter baumannii* Vaccine Candidates and Drug Targets in Recent Years

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In parallel to the uncontrolled use of antibiotics, the emergence of multidrug-resistant bacteria, like *Acinetobacter baumannii*, has posed a severe threat. *A. baumannii* predominates in the nosocomial setting due to its ability to persist in hospitals and survive antibiotic treatment, thereby eventually leading to an increasing prevalence and mortality due to its infection. With the increasing spectra of drug resistance and the incessant collapse of newly discovered antibiotics, new therapeutic countermeasures have been in high demand. Hence, recent research has shown favouritism towards the long-term solution of designing vaccines. Therefore, being a realistic alternative strategy to combat this pathogen, anti-*A. Baumannii* vaccines research has continued unearthing various antigens with variable results over the last decade. Again, other approaches, including pan-genomics, subtractive proteomics, and reverse vaccination strategies, have shown promise for identifying promiscuous core vaccine candidates that resulted in chimeric vaccine constructs. In addition, the integration of basic knowledge of the pathobiology of this drug-resistant bacteria has also facilitated the development of effective multiantigen vaccines. As opposed to the conventional trial-and-error approach, incorporating the *in silico* methods in recent studies, particularly network analysis, has manifested a great promise in unearthing novel vaccine candidates from the *A. baumannii* proteome. Some studies have used multiple *A. baumannii* data sources to build the co-functional networks and analyze them by k-shell decomposition. Additionally, Whole Genomic Protein Interactome (GPIN) analysis has utilized a rational approach for identifying essential proteins and presenting them as vaccines effective enough to combat the deadly pathogenic threats posed by *A. baumannii*. Others have identified multiple immune nodes using network-based centrality measurements for synergistic antigen combinations for different vaccination strategies. Protein-protein interactions have also been inferred utilizing structural approaches, such as molecular docking and molecular dynamics simulation. Similar workflows and technologies were employed to unveil novel

A. baumannii drug targets, with a similar trend in the increasing influx of *in silico* techniques. This review integrates the latest knowledge on the development of *A. baumannii* vaccines while highlighting the *in silico* methods as the future of such exploratory research. In parallel, we also briefly summarize recent advancements in *A. baumannii* drug target research.

Keywords: *Acinetobacter baumannii*, vaccine candidate, chimeric vaccine, ghost vaccine, drug target, *In silico* methods, bioinformatics, interactome analysis

INTRODUCTION

As one of the dreadful ESKAPE pathogens, *A. baumannii* has become a worldwide threat due to its resistance to a broad spectrum of currently available drugs, especially in the nosocomial setting (1). This is evident from the enormous mortalities of immunocompromised cases (2, 3) by this opportunistic pathogen. For example, a systematic statistical meta-analysis published in *The Lancet* reported *A. baumannii* as one of the six leading pathogens causing mortalities due to drug resistance, of which carbapenem-resistant *A. baumannii* has caused at least 50,000 deaths globally in the year 2019 (4). Moreover, the healthcare crisis caused by *A. baumannii*, especially the carbapenem-resistant strains, has peaked in intensive care units (ICU) synchronously with the COVID-19 pandemic (5, 6). Therefore, in parallel to the relentless drug resistance acquisition in *A. baumannii* towards currently available antibacterial drugs, biomedical research in discovering novel vaccines and drug targets remains exigent (7, 8).

Novel vaccine and drug development often require decades or even centuries (9, 10). Reportedly, there are no vaccine candidates for *A. baumannii* that have stepped into clinical trials (11–14). For vaccine candidates to step into clinical studies, assessing their *in vivo* reactogenicity and immunogenicity in animal models becomes mandatory (15). In addition, the pharmacological and toxicological properties of the targeted vaccine candidates are investigated along with the preclinical studies. Additionally, drug target selection, serving as the first and the most crucial step into drug development, is always supported by prior knowledge and robust characterisation of the proteins of interest or their related biological pathways from the scientific literature (16). The preliminary tests of a drug target's viability include knockout and expression studies of the targeted gene under stress, both for *in vivo* and *in vitro* models (16, 17).

In the light of the rapid development in multi-omic methods, as well as databases curated thereof, the contribution of bioinformatics based studies has been ubiquitous in research efforts on combating multidrug-resistant bacteria (18–21). For instance, by analysing the bacterial genome or proteome *via in silico* approaches such as protein interactome analysis, one can unveil novel crucial proteins in the bacteria of interest, which can potentially be vaccine candidates (22–24). With the increasing entries in experimentally validated 3D structure database, scilicet Protein Data Bank (PDB), the strength of interactions between small molecules and proteins, as well as protein-protein

interactions, can now be predicted *via in silico* approaches (25–27). Such a technique has also been employed in vaccine research by computationally inferring peptide-binding onto immune cell receptors (28). Almost similar methods are seen in the *in silico* drug target research. For example, virtual screening of large chemical databases on drug-target of interest can unearth novel antibacterial drugs to be repurposed or further developed (29, 30).

Exploring novel vaccine candidates or streamlining antigenic peptide regions through experimental screening on animal models is tremendously cost and time expensive; therefore, bioinformatics tools in aiding *in silico* vaccine design have been numerous and extensive (31, 32). Linear B- and T-cell epitope prediction tools, such as EpiJen, MHCpred, and NetMHC, have been prevalent and well-recognised as upstream exploratory research in vaccine design (33–35). Moreover, researchers have also developed bioinformatic tools to predict the allergenicity and toxicity of vaccine candidates, such as AllergenFP and ToxinPred, respectively (36, 37).

Over the years, bacteria have gained resistance to the newly developed drugs at a breakneck speed. Consequently, recent exploration favours escalating vaccine research rather than unveiling novel drug targets (38). This review summarizes the recent advancements in *A. baumannii* vaccine design (**Figure 1**). In concordance with the recent studies' heavy use of computational methods, we accentuate bioinformatics as the future of exploratory research in shepherding drug target selection and vaccine candidature and the multitudinous influx of novel insights into its implication. Moreover, we also briefly discuss *A. baumannii* drug target research, which acts as a temporary coping while we wait for the new vaccines to arrive.

INFERRING NOVEL VACCINE CANDIDATES FROM LABORATORY MEANS

Conventional means of inferring novel vaccine candidates require prior established knowledge of the proteins or metabolic pathways of interest and often involve in-depth characterisation of the potential proteins of interest. In addition, deducing new vaccine candidates *via* laboratory means often involves animal models; thus, initial molecular characterisation is almost necessary (39).

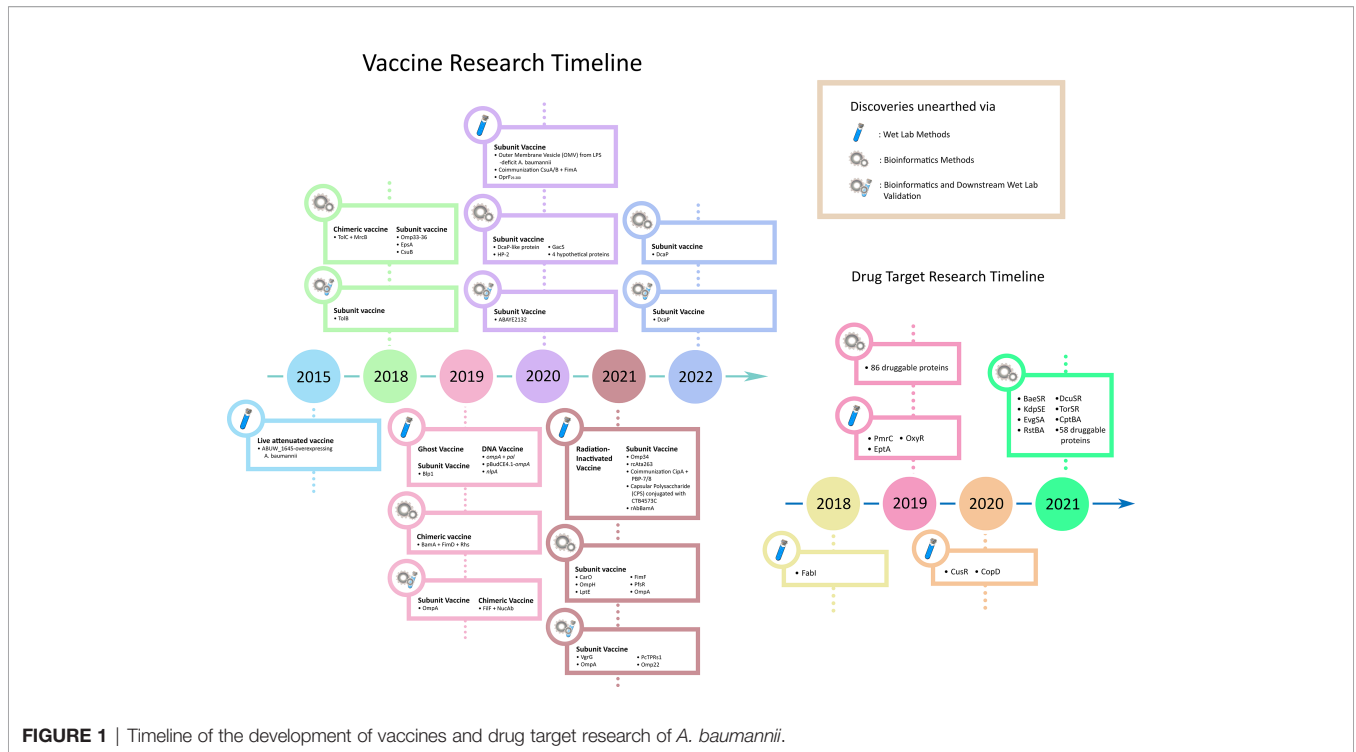


FIGURE 1 | Timeline of the development of vaccines and drug target research of *A. baumannii*.

Advancements in Vaccines Derived From Whole-Cell or Anatomical Components

Live vaccines are the most immunologically representative units in establishing vaccination despite posing a danger in regaining infectivity (40). Sequential intraperitoneal immunisation, with sub-lethal doses of different *A. baumannii* strains, has elicited antibody responses towards antigens of multiple strains in CD1 mice (41). Furthermore, a study on virulence switch in *A. baumannii* has highlighted the overexpression of a TetR-type transcriptional regulator, *ABUW_1645*, that facilitated the transformation of the cellular stage from virulent opaque (VIR-O) to avirulent translucent (AV-T) while proposing the potential of *ABUW_1645*-overexpressing *A. baumannii* to be utilized as a live-attenuated vaccine (42).

Bacterial outer membrane vesicle (OMV) has been an attractive vaccine candidate as it contains the outer membrane proteins (43). As lipopolysaccharide (LPS) is abundant in OMV, a study on the efficacy of OMV vaccine on LPS-deficit *A. baumannii* has disproved the effect of LPS on OMV production through electron microscopy (44, 45). In addition, the study also reported similar immunisation strength between OMV isolated from wild-type and purified LPS supplemented LPS-deficit *A. baumannii* by conferring complete protection to the C57BL/6 mouse model (44).

Like inactivated vaccines, bacterial ghosts are gram-negative bacteria depleted of their cytoplasmic and genetic constituents through E-mediated lysis, leaving only the cell envelopes (46). A study on the effectiveness of *A. baumannii* ghosts in conferring vaccinated protections in Sprague-Dawley rats has suggested promising results in terms of effectiveness and safety on

various administration methods, including subcutaneous, intramuscular, and intraperitoneal injections (47).

The replicative ability of bacteria can be disabled through the depletion of nucleic acids *via* gamma radiation exposure, with the protection by a specific antioxidant cocktail, and hence eventuating whole-cell inactivated vaccine with better immunogenicity than chemically inactivated vaccines (48–50). Studies showed that intranasal administration of radiation-inactivated *A. baumannii* grown *via* either planktonic cultures in rich media or biofilm cultures in static cultures underneath M9 media had conferred good protection in both healthy and neutropenic mouse models (51).

Novel Breakthroughs in Subunit Vaccine Research

Due to their safety and stable nature in various conditions, subunit vaccines have been ubiquitous in vaccine design studies (52, 53). Due to the crucial role of Omp34 in enhancing *A. baumannii* virulence and fitness, the Omp34 subunit vaccine has been proposed and reported to be protective in the BALB/c mouse model (54). The 263 amino acid long C-terminal end of an essential *A. baumannii* virulence factor, Ata (*rcAta*₂₆₃), has elicited immune protection *via* subcutaneous, intraperitoneal, and intranasal challenge in the BALB/c mouse model (55). The combination of two recombinant pilus proteins, namely CsuA/B and FimA, administered *via* subcutaneous injection, has been reported to confer partial (62%) protection in the BALB/c mouse model (56). The subcutaneous co-immunisation of two outer membrane serum resistance factors, CipA and PBP-7/8, has also conferred

80% protection in the C57BL/6 mouse model from the lethal dose *A. baumannii* challenge (39). Moreover, intramuscular injection and passive immunisation of a 711-aa long C-terminal fragment of *A. baumannii* Blp1 protein have protected the lethal challenge in the BALB/c mouse model (57).

As a crucial component on bacterial surfaces, polysaccharides serve as attractive targets for vaccine design. As polysaccharides alone do not elicit an adequate immune response, the conjugation of carrier proteins is often required (58). Upon misuse of antibiotics, *A. baumannii* can produce capsular polysaccharides (CPS) to enhance antibiotic resistance and virulence (59). By introducing the O-glycosylation system from *Neisseria* into *A. baumannii*, a resulting *in vivo* produced bioconjugated vaccine, having *A. baumannii* CPS and recombinant cholera toxin B subunit (CTB^{4573C}) and aluminium hydroxide adjuvant, was reported to manifest good protection and safety in the BALB/c mouse model (60).

By injecting DNA coding for immunogenic antigens into the host *via* a plasmid, immune protection from vaccination can be expected through antigenic expression by host cells (61). Intramuscular injection of DNA vaccine encoding *A. baumannii* OmpA and Pal, adjuvanted by CpG oligodeoxynucleotides (CpG ODN), into C57BL/6 mice exhibited immunological protection against clinical strains of *A. baumannii*, driven by adaptive immune response activation (62). Another study has also designed and proposed the *A. baumannii* OmpA-derived DNA vaccine, pBudCE4.1-*ompA*, as protective against lethal-dose challenge in the BALB/c mouse model (63, 64). Intramuscular injection of *nlpA* DNA vaccine into BALB/c mouse model has also successfully elicited an immune response in a study by Hashemzahi et al. (65). With the recently claimed success of the mRNA vaccine in controlling the coronavirus disease 2019 (COVID-19) pandemic, one can explore the feasibility of the *A. baumannii* mRNA vaccine in the future (66).

Due to the high conservation of specific essential genes across different bacterial species, cross-reactivity of subunit vaccines derived from these genetic sections occurs. For example, a study utilizing the Swiss albino mouse model showed the feasibility of *P. aeruginosa* N-terminal OprF (OprF₂₅₋₂₀₀) adjuvanted with Bacillus Calmette-Guerin (BCG) and aluminium hydroxide in conferring cross-reactive immunisation to both *P. aeruginosa* and *A. baumannii* (67). Another study proposed recombinant *A. baumannii* BamA (rAbBamA) protein as a potential vaccine candidate *via* intramuscular challenge on C57/BL6 mouse model adjuvanted by aluminium hydroxide, while reported potential cross-reactivity across *K. pneumoniae* and *E. coli* *via* immunoblot assay of anti-rAbBamA (68).

IN-SILICO METHODS IN DRIVING EXPLORATORY RESEARCH ON NOVEL VACCINES

With the rapid advancement of bioinformatics in extracting and predicting multi-omic information, as well as the expansion of proteomic and genomic databases, research attempts in

unearthing vital proteins as novel vaccine candidates have become meagre cost and increasingly prevalent (69–71). By mapping small protein interactomes (SPIN) of virulent factors, vaccine candidates, and key factors retrieved from literature onto the whole genome protein interactome (GPIN), a study has reported crucial proteins *via* co-functional network analysis and k-shell decomposition, which can serve as potential vaccine candidates (22). Besides, a theoretical study on hypothetical proteins (HPs) in 30 multidrug-resistant *A. baumannii* strains has proposed 4 HPs as potential vaccine candidates *via in silico* immunological analyses (72). In addition, utilizing *in silico* functional analysis, the authors also proposed the druggability of 7 HPs. Upstream subtractive proteomics, combined with linear T and B cell epitopes prediction, structural screening with immune cell receptors, and druggability analysis, have finalised a chimeric subunit vaccine candidate derived from TolC and MrcB in *A. baumannii*, as well as 13 potentially druggable proteins (73).

Immunoinformatics and Proteomics in Vaccine Design

Bioinformatics approaches, especially proteomics, have been extensively applied in recent studies by ushering the mining of core protein candidates in downstream vaccine design and modifications (Figure 2). For instance, applying pan genomics in inferring gene conservation across species or strains (74), predicting immunogenicity in proteins and inferring epitopes through reverse vaccinology (75), and inferring essential proteins involved during infection *via* proteomic interactomes (76, 77). Furthermore, predicting effective T and B-cell epitopes has been an essential step during vaccine design in ensuring that only the specific immunogenic parts of the candidate proteins are retained *via* peptide truncation due to cost and time efficiency in laboratory or downstream bulk production (78).

A study has applied reverse vaccinology to 33 genomes of *A. baumannii* strains, and downstream B-cell epitope analysis has indicated the potential of two outer membrane proteins, scilicet a DcaP-like protein and HP-2, a novel hypothetical protein, as vaccine candidates (79). Moreover, Beiranvand et al. has integrated the predicted protein and epitope topology on the bacterial membrane surface to the usual vaccine design workflow, namely B cell epitope, subcellular, antigenicity, and solubility predictions, and finalised with CarO, OmpH, LptE, FimF, and PfsR as top five *A. baumannii* vaccine candidates (80, 81). Furthermore, linear prediction of epitopes and their properties has also been conducted on GacS, a virulence modulator *via* citrate metabolism pathway, resulting in five peptides being proposed as *A. baumannii* vaccine candidates (82).

Genomic and proteomic sequence analyses have been employed to search for the conserved sequence to serve as vaccine candidates. Following transcriptional characterisation of *A. baumannii* Omp33-36 protein to highlight its role during the initial phase of infection, phylogenetic analyses have revealed an 8-aa highly conserved motif (PLAEAAFL), potential enough for vaccine development processing (83). Moreover, comparative genomics on *A. baumannii* OmpA of different strains, with downstream *in silico*

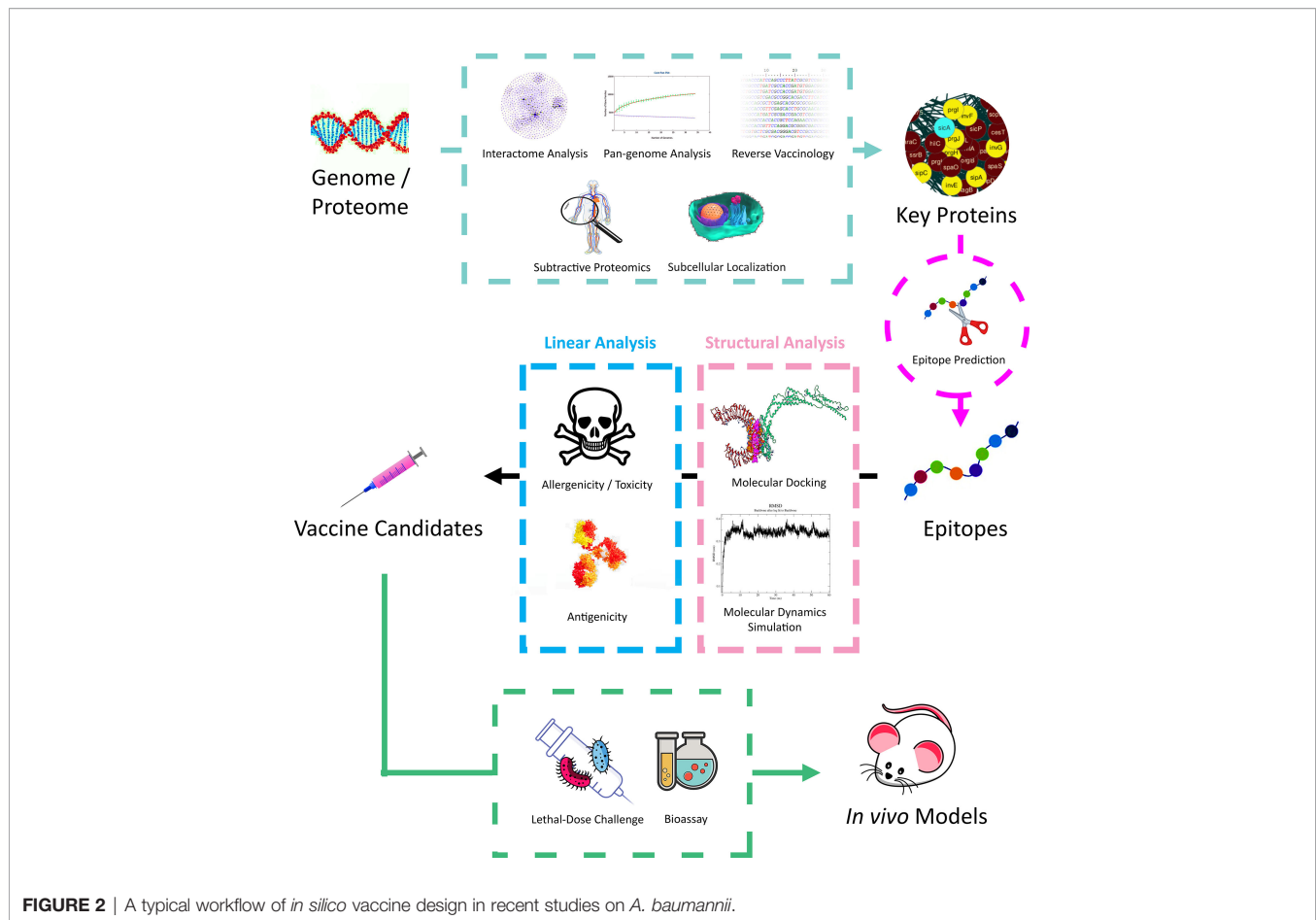


FIGURE 2 | A typical workflow of *in silico* vaccine design in recent studies on *A. baumannii*.

prediction of T and B cell epitopes, as well as *in silico* characterisation and molecular docking with TLR-2, has derived a 25 amino acids long vaccine candidate by Sogasu et al. (84). Furthermore, another study has demonstrated the integration of pan genomic analysis of around 4200 genomes, T and B cell epitope predictions, and network-based centrality methods in identifying multiple immunologic nodes in *A. baumannii*, which can result in the elucidation of combinatorial synergy in different antigens for different vaccination strategies (85).

In addition to linear prediction of T and B cell epitopes, structure-based downstream analysis, such as structure modelling, molecular docking, and molecular dynamics (MD) simulation, has been integrated to confer more robust computational insights. For example, utilizing T and B cell epitope prediction, immunological feature screening, molecular docking with immune cell receptors, and downstream integration of *in silico* gene cloning, a multi-epitope vaccine design has been proposed computationally from *A. baumannii* CarO, an outer membrane protein associated with carbapenem resistance (86). Again, utilizing a similar approach, Khalid et al. has also proposed an *in silico* designed vaccine derived from *A. baumannii* DcaP protein (87).

More comprehensive *in silico* approaches have also been conducted in vaccine design. For instance, upstream integration

of pan genomics, subtractive proteomics, and reverse vaccinology into T and B cell epitope prediction, pipelined with downstream *in silico* immunological simulation and structure-based screening onto immune cell receptors, two *A. baumannii* multi-epitope vaccine constructs with good safety profiles have been designed (88). Another study on Tigecycline-resistant *A. baumannii* utilized subtractive proteomics, exoproteome and secretome predictions, interactome analysis, as well as other physicochemical and immunological predictions to propose a chimeric vaccine design. The vaccine's predicted T and B cell epitopes are from three proteins, scilicet BamA, an outer membrane protein assembly complex, FimD, an outer membrane usher protein, and Rhs, a type IV secretion protein (89). An integrated approach of extracting *A. baumannii* virulent factors from the VFDB database, secretome and exoproteome analysis, subtractive proteomics, B and T cell epitope prediction, as well as peptide docking analysis, has resulted in two nine amino acid long potential vaccine candidates derived from EpsA and CsuB, respectively (90).

To facilitate *ex silico* robustness of computationally predicted results, downstream *in vitro* and *in vivo* models have been utilized. For example, predicted T and B cell epitopes of an *A. baumannii* outer membrane protein, TolB, were verified to be antigenic *in vivo*, by utilizing lymphocyte proliferation assay and

ELISA, respectively, in a mouse model (91). In another study on the feasibility of vaccine design based on VgrG, a type VI secretion system (T6SS) component, the immunisation of two peptides derived from *A. baumannii* VgrG conserved sequences (*vgrG*₁₁₅₉₋₂₁₉₆ and *vgrG*₁₁₅₉₋₁₅₀₂) in BALB/c mice has conferred protection from lethal-dose challenges (92). Again, ABAYE2132, an *A. baumannii* fimbrial protein previously proposed *via* reverse vaccinology, has been translated into an animal study, and its protection capability towards subcutaneously injected BALB/c mouse model was conferred *via* lethal-dose challenge (93). Moreover, a study has proposed a novel synthetic peptide derived from *A. baumannii* OmpA protein using the overlapping regions of predicted T and B cell epitopes, pipelined with three-dose subcutaneous injection in C5BL/6 SPF mouse model, which eventually observed spiked antibody production in the injected mice (94). Another study on the *A. baumannii* OmpA protein has proposed a 27 amino acid long peptide as a vaccine candidate by manifesting protection towards the challenge in C5BL/6 mice (95). Moreover, a recombinant multi-epitope protein has been designed from predicted T and B cell epitopes of *A. baumannii* outer membrane proteins, namely FilF and NucAb, which conferred immunogenicity and protection in the BALB/c mouse model (96). Similar approaches have been adopted by Raoufi et al. on DcaP, a porin protein in *A. baumannii*, which has manifested protection against the challenge in BALB/c mice (97). Furthermore, Abdollahi et al. named a previously hypothetical protein in *A. baumannii*, PcTPRs1, and derived a 101 amino acid long subunit vaccine based on its *in-silico* predicted T and B cell epitopes, subcellular locations, physiochemical properties, as well as *in vivo* challenge on BALB/c mouse model supplemented by Freund's adjuvant *via* subcutaneous injection (98). Recently, the *A. baumannii* recombinant multi-epitope Omp22 vaccine derived from its predicted T and B cell epitopes, with chitosan and poly lactic-co-glycolic acid (CS-PLGA) nanoparticles encapsulation, has been proposed as a potential nanovaccine candidate with reported protection towards lethal intratracheal challenge on BALB/c mice (99).

In Silico Methodologies to Nominate Vaccine Candidates

With the surfacing of more sophisticated bioinformatics tools over the recent years, *in silico* approaches in unveiling potential vaccine candidates within the *A. baumannii* proteome have become highly diverse. However, it can be stratified into two major categories: the upstream and the downstream analysis. The upstream analysis of vaccine candidature aims to mine a subset of potential candidates from a vast pool of proteins, usually the whole proteome, genome, and pan-genome. Furthermore, the downstream analysis aims either to shape the protein candidates into effective epitopes or to validate the feasibility of the proposed vaccine candidates, *albeit* computationally.

The upstream analysis of *in silico* vaccine candidature includes protein interactome analysis, which rationally helps to unearth the protein central to the interactome and thus, plays a crucial role in the pathogenesis/pathophysiology of the disease (22). Therein, the connectivity between each protein can be

extracted from the protein interaction metadatabase like STRING (100), while network visualisation software tools and plugins like Cytoscape (101), CytoNCA (102), and NetworkAnalyzer (103) help in the analysis. Other analyses, such as *k*-core analysis, can be conducted externally using MATLAB (104). The pan-genome analysis allows the analysis of inter-species or -strain gene conservation, thus eventuating vaccine candidates with a broad spectrum of targets and high tolerance towards mutation. Such analysis can be done *via* the Bacterial Pan Genome Analysis Tool (BPGA) (105) and PanRV pipeline (106). Subtractive proteomics inspects the homology of the target proteome of interest with the host proteome, for example, the *A. baumannii* proteome and human proteome, to avoid integration into the host genome. This can be achieved using the BLASTp tool accelerated with in-house scripts (90). Predictions on the properties of the proteins of interest, such as subcellular localisation of proteins and signal peptides, can be vital in reverse vaccinology. Protein subcellular localisation can be predicted *via* PSORTb (107), CELLO (108), PSLpred (109), and Gneg-mPLoc (110), while the signal peptides localisation can be predicted *via* SignalP (111).

One significant component of the downstream analysis is T and B cell epitope prediction; such bioinformatic tools include ABCPred (112), ProPred (113), as well as IEDB tools such as Discotope (114), ElliPro (115), and TepiTool (116). The predicted epitopes are sometimes backed up by external antigenicity prediction tools, such as Vaxign (117), ANTIGENpro (118), and Vaxijen (119). Safety profiles prediction, such as allergenicity of the predicted epitopes, can be conducted using AllergenFP (36) and AlgPred (120). Besides, ToxinPred (37) gives an idea of the related toxicity. Physiochemical properties such as molecular weight, stability, and hydropathicity, can be predicted using the ExPasy ProtParam server (121). The binding capabilities of epitopes to immune cell receptors can also be predicted using the structural method. For instance, the 3D structure of the epitopes can be predicted using I-TASSER (122) and SWISS-MODEL (123). Peptide docking tools such as HADDOCK (124), FireDock (125), and PatchDock (126) can predict epitope binding strength onto immune cell receptors. Eventually, the epitope binding dynamics can be simulated through MD simulation method *via* GROMACS (127).

RECENT RESEARCH ON VALIDATING NOVEL DRUG TARGETS

Aside from all the hype on vaccine research, efforts in foraging novel drug targets remain inevitable and in tremendous demand prior to the approval, introduction, and global distribution of new vaccines into the human population.

Unearthing Drug Targets Using Conventional Means

Like vaccine research, unveiling novel drug targets *via* conventional laboratory approaches requires extensive

molecular knowledge or characterisation of the protein of interest or its biological pathway. Most frequently employed approaches in inferring drug targets include knockout study and chemical inactivation of protein function to inspect its essentiality in ensuring bacterial survival (128, 129).

Instead of exploring novel direct bactericidal drug targets, recent research has sought adjuvant therapy drug targets in the molecular components that contribute to bacterial virulence and drug resistance. For instance, colistin, or polymyxin E, has been a prominent final resort for severe *A. baumannii* infection, and its resistance is mediated by the *pmrCAB* operon, which codes for phosphoethanolamine (PetN) and two-component system (TCS), as well as PetN addition to the LPS lipid A (130). Moreover, a knockout study on colistin resistance has suggested PetN transferases, scilicet PmrC and EptA, as promising drug targets in attenuating colistin resistance in *A. baumannii* while disproving PmrA, a transcriptional regulator mediating PmrC overexpression, as a drug target due to its limited spectrum (131). Furthermore, utilizing a chemical scaffold compound that inhibits the enzymatic activity of FabI, FabI has manifested druggability in *A. baumannii* by enhancing the bactericidal effect of colistin (129).

Aside from attenuating drug resistance, attempts to promote bacterial susceptibility to the immune system have been observed in research studies. Notably, copper has been an interesting antibacterial molecule employed by the immune system to facilitate pathogenic clearance upon infection, manifested by a copper burst in macrophage phagosomes and blood (132–134). In this regard, Williams et al. has reported 11 proteins that result in *A. baumannii* sensitivity to copper upon loss-of-function mutations, with two of them, scilicet CusR and CopD, being validated in the BALB/c mouse model in causing less mortality (135). These proteins rendering copper resistance could serve as potential drug targets in weakening *A. baumannii* virulence. Again, another study has proposed the druggability of OxyR, a transcriptional regulator in hydrogen peroxide detoxification, *via* a knockout study (128). Additionally, through *in vivo* imaging, the authors have supplemented the finding that *A. baumannii* in the lung suffers oxidative stress from hydrogen peroxide.

***In-Silico* Methods in Mining Novel Drug Targets**

With the enormous growth in the variety and size of biological databases, different databases have been innovatively extracted in inferring drug targets. Potentially bactericidal drug targets burrowed in vast and complex datasets could be unearthed with comprehensive analyses on annotated multi-omic sequences (**Figure 3**) (136). For example, in synchronous to the increasing attention towards the TCS in bacteria, pan-genomics and sequence variation analysis on TCS proteins in seven pathogen species, inclusive of *A. baumannii*, has been conducted by Rajput et al., who have reported BaeSR, KdpDE, EvgSA, RstBA, DcuSR, and TorSR as potentially druggable targets (137). Moreover, the Toxin-Antitoxin database (TADB) pipelined with comparative genomics and phylogenetic analysis, as well as *in vitro* transcriptional analysis upon oxidative and

antibiotic stress, has demonstrated the potential druggability of *A. baumannii* CptBA Toxin-Antitoxin system in disrupting intracellular toxin-antitoxin balance, hence eventuating cell suicide (17). Furthermore, integrated analysis of metabolic pathways and chokepoints *via* the KEGG database (138), plasmid proteins, virulence factors *via* the VFDB database (139), and drug resistance proteins *via* the CARD database (140), pipelined with subtractive analysis of essentiality and non-homology, Kaur et al. have presented 58 potentially druggable proteins of which eighteen (18) existed or had their homologs in DrugBank (141, 142). Additionally, utilizing KEGG pathway analysis, essentiality analysis from the DEG database (143), and subtractive proteomics, Uddin et al. have presented eighty-six (86) potentially druggable proteins, with forty-five (45) exhibiting high sequence similarity with the existing drug targets in DrugBank (144).

Besides the above, bioinformatics approaches downstream of drug target identification often include virtual screening *via* molecular docking and MD simulation, and hence, experimentally crystallised protein 3D structures have become a godsend in recent research (29, 30, 145). In this regard, in a study, researchers have crystallised the 3D structures of 29 essential proteins in *A. baumannii* and deposited them in Protein Data Bank (PDB), fifteen (15) of which were recommended to be druggable, based on active site features and sequence homology (146).

OTHER PROTEOMICS-DRIVEN STRATEGIES

Aside from the unveiling of novel vaccines and drug targets, recent proteomics research on other strategies such as antimicrobial peptides (AMPs) have been promising in combating *A. baumannii* (147). In a study by Jung et al., *in vivo* screening of AMPs in a mouse model has reported SMAP-29 and TP4 to exhibit prophylactic properties, while dC4 and dN4 exhibited potential therapeutic activity against *A. baumannii* (148). Moreover, a hexahistidine-tagged AMP, namely Lys AB2 P3-His, with a gold nanoparticle carrier, AuNP-Apt, has conferred significant protection to mice against lethal-dose *A. baumannii* challenge (149). Other than direct antimicrobial activities, the additional capabilities of AMPs in enhancing drug effects have been explored. Esc(1-21), a frog-skin AMP derivative, has manifested synergistic membrane-perturbing antibacterial activity with colistin on multidrug-resistant *A. baumannii* clinical isolates (150). *In silico* study on AMPs has been prevalent with the increasing availability of peptide-peptide docking. A virtual screening study by He et al. with a set of cyclic peptides against *A. baumannii* BamA, pipelined with downstream *in vivo* mouse model challenge, has proposed cyclo-RRWRRRW to be membrane-perturbing bactericidal (151). Another study has demonstrated the *in silico* screening of human proteome for encrypted AMPs to be translatable into *in vivo* mouse models (152).

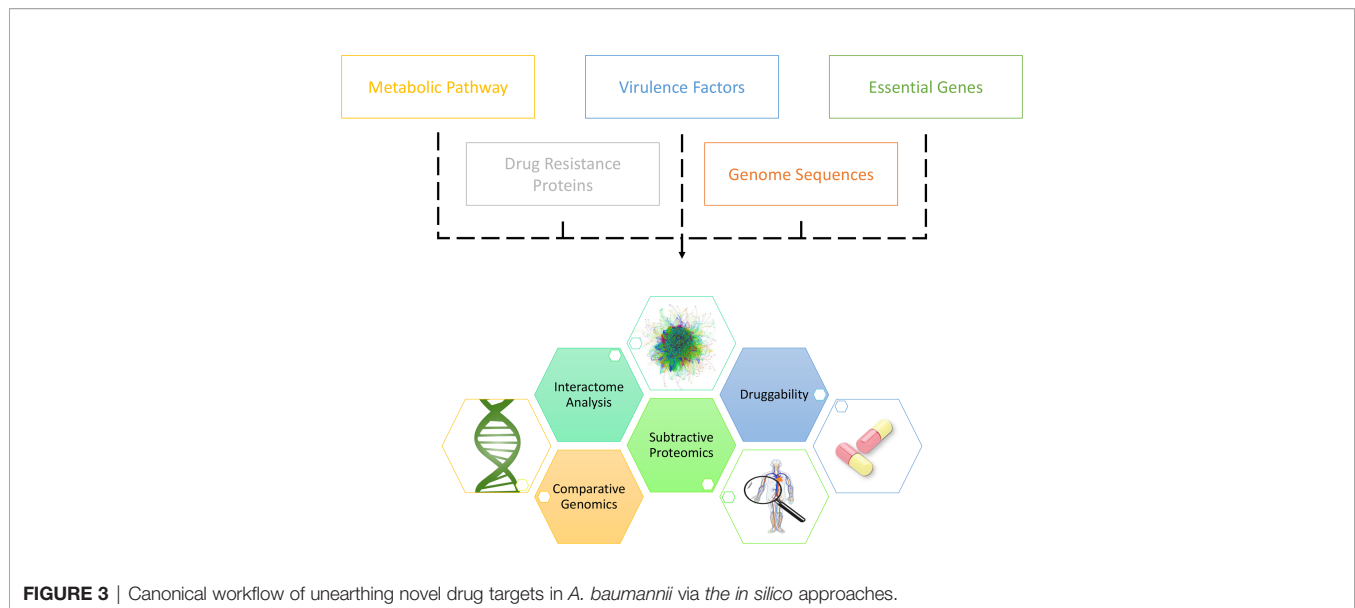


FIGURE 3 | Canonical workflow of unearthing novel drug targets in *A. baumannii* via the *in silico* approaches.

CONCLUSION

The increased utilization of bioinformatic approaches in exploring *A. baumannii* vaccines has invited a tremendous influx of passion and novel research outputs in combating the notorious nosocomial pathogen, mainly due to its immense cost and time efficiency. We can unveil potential vaccine candidates by extracting and collating information through different databases with statistical means. In addition to employing bioinformatics tools with straightforward outputs, supplementary approaches, such as comparative genomics, subtractive proteomics, and interactome analyses, have been conducted to strengthen or further streamline the shortlisted vaccine candidates. Similar research trends and methodologies can be observed in unveiling novel drug targets. In the light of the rapid expansion of drug resistance spectra in bacteria, scouring for novel vaccine candidates seemed to be a more attractive choice than tramping in the vicious cycle of bacteria rapidly acquiring drug resistance. Nonetheless, due to the long timeline of vaccine research, unearthing novel drug targets remains crucial while waiting for new

vaccines to be developed and distributed. As research progresses, bioinformatics databases and methodologies will continue to confer valuable insights in pushing through the vaccine research to combat the *A. baumannii* infection.

AUTHOR CONTRIBUTIONS

YT primarily wrote the manuscript aided by complete editorial up-gradation by CL. In addition, figures were generated by YT with guidance provided by CL. All authors contributed to the article and approved the submitted version.

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