International Journal of Drug Research and Technology

Available online at http://www.ijdrt.com

Review Article

A SYSTEMATIC REVIEW EXAMINING HOW 'OMICS ARE APPLIED TO DRUG DEVELOPMENT RESEARCH

Baldeep Singh Chowlia and **Craig Allan Russell***

Aston School of Pharmacy, Aston University, Birmingham B4 7ET, UK

ABSTRACT

Background: The development of a new drug can be a very time consuming and expensive process, which can take up to 15 years and cost billions of dollars. This review will explore the omics, in particular: genomics, proteomics, transcriptomics and metabolomics, and how they can be incorporated in drug development research.

Aim: Construct a comprehensive review exploring the benefits and drawbacks of applying the 'omics' to drug development research.

Method: A systematic literature search was conducted using appropriate databases. Only records published between the years 2013-2017 were used, with the words 'drug' and 'development' in the title and at least one of the relevant 'omics'. All records that were duplicates, not free full text articles or not written in English were excluded.

Results: After conducting the search 12 articles were found to meet to inclusion criteria. 'Omics was shown to be a valuable tool in: drug repositioning, reducing adverse drug reactions, predicting toxicology at early stages of drug discovery, personalised medication, understanding disease pathogenesis and decreasing the cost and time involved in the drug development process.

Conclusion: The 'omics can all be applied successfully to different parts of the drug discovery process. It was found that applying the 'omics could be used in finding new drug targets, understanding how diseases are developed and development of personalised medicine. The 'omics' also showed promise of cost-effectiveness over current methods of drug development.

Keywords: Genomics, Transcriptomics, Metabolomics, Proteomics, Pharmacogenomics, Individualised medicine, Personalised medicine.

INTRODUCTION

Rationale

Omics is the group of technologies which studies classes of molecules such as, genes, proteins, mRNA and metabolites. This review will explore the current trends in genomics, proteomics, transcriptomics and metabolomics, respectively. Each of these 'omics will be discussed in detail, giving a thorough insight to how they can be applied in drug development research, taking into consideration factors such as cost, time and the key advantages and disadvantages of each.

Historically drugs were discovered through trial and error of usually herbal based medicines, this was not only a very slow process but also potentially very dangerous, in addition to this the drug often helped symptoms of the disease rather than treating the disease itself (Boa, 2017). Examples of medicines which were used included, willow bark which was used to reduce fever and cinchona bark which was used to treat fever associated with malaria, even by the start of the 20th century the known chemicals used in medicine were for analgesia and anaesthetics only, there were no actual drugs to treat or cure disease (Boa, 2017). Physician Paul Ehrlich explained how it was possible to find a chemical that is able to kill a specific disease but not harm anything else in the patient's body, he described these chemicals as 'magic bullets' (Bosch and Rosch, 2008). In 1910 'Salvarsan' became the first fully synthetic drug, it was used to treat syphilis. From this discovery researchers than began to develop drugs specific to targeting the disease itself rather than treating symptoms (Bosch and Rosch, 2008).

With drug development today, there are three key parts to research involved in bringing a new drug to the market. The first part of research is known as drug discovery, which was conventionally done by phenotypic screening, this is where potential medicines are identified to see whether they can alter the phenotype of a cell or an organism in order to produce a desired effect which will stop or reverse the effects of a particular disease, this process usually takes two years (Elhassa and Alfarouk, 2015). Following drug discovery the drug then enters pre-clinical trials where the drug must got through *in vitro* and *in vivo* tests to find out if the drug has any toxicity issues, this is important as if these are not identified it can potentially lead to serious harm in patients (Fda.gov, 2015). This part of the drug development process can take a further four years (Elhassa and Alfarouk, 2015). The drug must then enter clinical trial phases and progress through parts I, II and III which usually takes another seven years, only then can the drug be presented to the FDA for approval (Elhassa and Alfarouk, 2015). This process costs billions of dollars and with the success rate of drugs gaining approval being only around 8%, there is a strong demand for improvement (Fdareview.org, 2016). This review will provide a thorough examination of existing literature

to generate a clear understanding of how ‘omics can be used to save time and capital in this process.

Two issues which are a cause for concern in medicine today include the rising prevalence of drug resistant diseases and undesired drug side effects, these issues can be addressed in the drug development process before the drug even reaches the market. In the case of adverse side effects of drugs this review will explore how ‘omics can be used to overcome any potential side effects or even pre-empt which drugs would give such side effects and thereby preventing late failures. One study suggests pharmacogenomics has the potential to decrease side effects by 25%-50% (Arnaout *et al.,* 2013). With regards to with drug resistant diseases, an insight will be given as to how ‘omics can be applied to not only find new drug targets, but to also give and understanding to why the disease may have initially become resistant. Furthermore, with an increase of chronic diseases there is evidently and increased demand for newer medicines, this review will also explore how ‘omics can be incorporated in drug development research to ensure this demand is met in the growing market.

Additionally, with the clear benefits of personalised medicine and the need to treat patients as individuals rather than a population, ‘omics can be used to incorporate this in day to day prescribing. An example of this is warfarin dosing based on the CYP2C9 gene (a gene involved in the metabolism of warfarin), polymorphisms in this gene reduce warfarin metabolism (Chong, 2015). In light of this discovery, studies have been conducted to assess the benefits of clinical applications of genetics testing before anticoagulation therapy. It was found that although there is benefits to genetic testing there is not yet sufficient evidence to support the use of the application outside of clinical trials (Kangelaris, *et al.,* 2009). If future studies are successful in closing the evidence gap, this will enable more precise dosing and prevent bleeding. Clearly showing that how ‘omics can be incorporated in personalised medicine. Building on this, this review will also explore examples of how useful the ‘omics can be when personalising medicine and drug regimens.

AIMS AND OBJECTIVES

This review seeks to produce a detailed comprehensive document mapping the current trends in applied 'omics approaches on the recent landscape of drug development research. This review will consider the areas of genes (genomics), mRNA (transcriptomics), proteins (proteomics) and metabolites (metabolomics).

Objectives

- Determine the cost effectiveness of using ‘omics in drug development research
- Determine which area of ‘omics is most currently researched upon and reasons why this may be
- Compare and contrast the current methods of drug development research to those used historically
- Search relevant literature on ‘omics in drug development research on available databases

METHODS

A systematic review was conducted in order to ensure that the highest amount of studies could be included in this document, in addition to this a systematic review would offers the most evidence in terms of research. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to when assessing literature for eligibility (PRISMA, 2009). To construct the review the PRISMA checklist was used to ensure the review if of a good structure and quality (PRISMA, 2009).

Method for Literature Search

The databases used to search for data were; Scopus, Web of Science, Google Scholar, PubMed and the Cochrane Database of Systematic Reviews. In order to find all relevant literature, initially all basic search terms where used in the databases, the following terms were searched individually, ‘omics, genomics, proteomics, transcriptomics, metabolomics, lipidomics, foodomics, drug development, medicine and research. Following the initial searches, terms where then combined until an appropriate final search term was found to be the most fitting, this term was, ‘(Drug development OR Medicine) AND (Research) AND ('omics OR genomics OR proteomics OR transcriptomics OR lipidomics OR foodomics)’, this was adjusted appropriately for each database.

Then finally, the years for which articles that would be included were restricted from 2013 to 2017, this was to make sure the most recent literature would be included in the review. In addition to this, all studies that were not human studies were excluded, as was all literature that was not written in English.

Literature Screening using PRISMA

Following broad identification of relevant literature, the PRISMA flow diagram was followed to help screen the records in a systematic manner to improve the specificity of records. Firstly any duplicates of articles were removed, following this titles of records were screened to assess suitability, an example being if a title focussed on drug development technologies other than those which included any one of the 'omics, the record would be discarded. Out of the remaining articles, the abstracts were analysed to make sure the article was relevant and could be used in this review.

Meta-Analysis

Although a meta-analysis would help bring forward a statistically valid conclusion, for this review a meta-analysis could not be conducted. This was because the articles found (using the search strategy described) did not contain sufficiently homogenous data to allow reliable comparisons to be drawn. Instead, each of the 'omics has been analysed individually on how they are incorporated in drug development research and a qualitative synthesis of each of the articles has been conducted.

Assessing Risk of Bias

In order to assess the risk of bias in certain studies, which were included in this paper, the JADAD scale was used to assess the trials included in this review (Jadad et al., 1996). The JADAD scale is easy to use, reliable and has external validity. Three items are assessed using this scale these are: randomization, blinding and the account of withdrawals and dropouts. Points were given for each item to calculate the risk of bias. Scores of 1-2 are understood as a high risk of bias, whilst a score of 3 is understood as a moderate risk of bias and a score of 4-5 is understood as a low risk of bias (Jadad et al., 1996).

RESULTS

After using the final search term an initial total of 489 records were identified through the databases described above. After duplicates of the same articles were removed and a screening of the titles, a number of 56 records remained. Further articles where then removed as they were found not to be suitable or available to access. Leaving a final number of 12 articles to be included in this review. The PRISMA flowchart illustrating the literature handling process can be seen in figure 1 below.

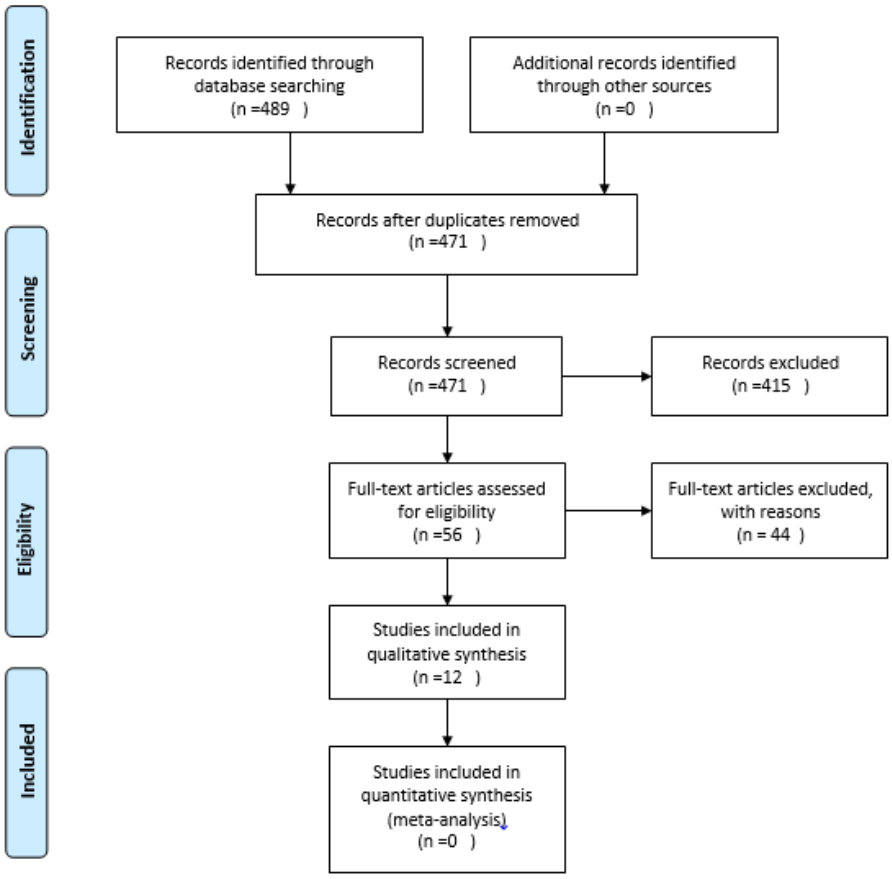

Figure 1: PRISMA flowchart, which demonstrates how the articles found using the search strategy, mentioned above, would go through a process of inclusion/exclusion to leave only those records which were eligible for this review.

After conducting the search strategy described above, the final 12 records found were all individually analysed to see how they described the 'omics to be used in drug development research. The table below summarises the key data extracted from the included studies (Table 2).

Genomics

In regards to genomics, Simonds et al., 2013 conducted a comparative effectiveness research (CER) was conducted to explore genomics in personalised medicine. The study suggests genomics medicines in clinical practice is actually being held back by lack of evidence in the field which suggests there still needs to be work done in this field. The biggest challenges described in the study were the implementation of genomics in to clinical practice. Research suggested that not only was there evidence gaps which prevented this but the current regulatory structure focuses on analytical accuracy rather than clinical

validity/usefulness and this creates the potential that genomics tests could be implemented into clinical practice without sufficient benefit over the current standard care. However, in the same study a project title which compared the effectiveness in genomic and personalised medicine for colon cancer, conducted a microsimulation to estimate the impact of specific gene testing (KRAS gene and BRAF gene), it was found that testing for KRAS and BRAF mutation improves the cost effectiveness of anti-EGFR therapy, but the actual cost effectiveness was still above the $100000/quality-adjusted-life-year (Simonds *et al*., 2013).

Another genomics study explored how adverse outcomes can be avoided through pharmacogenomics by choosing and dosing of existing drugs through looking at a person's genomic variants. A Monte Carlo model was used in a study, (Arnaout *et al*., 2013)), to predict time and cost of using genomics to reduce adverse drug outcomes. Figure 1, shows a graph presenting the results of the Monte Carlo prediction on the cost of research for developing clinically validated pharmacogenomics guidelines (green, left axis) and the cumulative decrease in adverse outcomes to which they would lead when implemented (blue, right axis). The studies model found the development of guidelines could reduce adverse outcomes by 25%-50% and take 20 years, but implementing pharmacogenomics projects could speed up the process (Arnaout *et al*., 2013). The use of personalised medicine offers an improvement in risk assessment, diagnosis, prognosis and treatment, this can be enhanced by genomics (Tremblay and Hamet, 2013).

Lefant (2013) also employed genetic profiling, which suggested that only genetic variants, which are shown to give a variable drug response, should be used in clinical application. As a result of this, the article looked in to statins and clopidogrel,, they found that at least one variant in the gene SLCO1B1 can increase the risk of myopathy when taking statins by 15% in homozygote carriers of the allele, whereas only a risk of 1.4% in heterozygote carriers. In addition to this in the case of clopidogrel (a prodrug) it was found that variants of the enzyme CYP2C19 (enzyme required to activate clopidogrel) could in fact alter the effect of the drug (Lefant, 2013).

An investigation was conducted by Wang and Guda (2016), to explore how 'omics could be used in order to find therapeutically targets for triple negative breast cancer were found in another article. The study found that using genomics, hyperactivated genes in triple negative breast cancer were identified, which enabled a better understanding of the pathogenesis of the cancer. Table 3 below gives a list genomic profiles for targets of agents that are already being explored in clinical trials. Potential molecular targets for the disease were also found, these included; FGFR2, MAPK13, TP53, SRC family, MUC family, BCL2 family, CSF1R, EPHB3, TRIB1 AND LAD1. It was found that some of these targets have also been suggested by different methods of target discovery, whilst other offers much promise as new targets for treatment of the disease (Wang and Guda, 2016).

The application of genetic profiling in cancer treatment was also explored (Uzilov, *et al.,* 2016). The study created a personalised cancer therapy (PCT) program based on a genomic approach, this was to fully portray the complexity of each tumour. The number of mutations, drug recommendations and alterations was compared to other methods of approach such as the: CHPv2 and Oncomine Cancer Panel and FoundationOne systems. The results of the study indicated that using the PCT cancer-relevant somatic mutations per patient were identified 13.3 fold, 6.9 fold and 4.7 fold more than in comparable methods, respectively. In addition to this actionable alterations were found in 91% of patients, 7.5 fold, 2.0 fold and 1.9 fold increase over those described (Uzilov *et al.,* 2016)

Proteomics

The same search strategy was used to find studies which incorporated proteomics. A study conducted (Lindhart, *et al.*, 2016) looked in to, the use of proteins as biomarkers which would enable earlier detection of potential renal failure. The study looked at the protein SKD273 which has shown potential to identify normoal buminuric diabetic patients who later progress to overt kidney disease. If the protein is found to be a successful biomarker, it holds the potential of allowing treatment to begin at a much earlier point for high risk patients and therefore offering earlier renoprotective treatment. Another benefit to the study is even if the CKD273 classifier is not found to be a successful as a biomarker, the study also includes a control group of patients taking spironolactone, and this could show the benefits of the drug in early intervention of diabetes (Lindhart *et al.*, 2016).

Tenga and Lazar (2014) studied the proteins, which are expressed in the G1-Stage of breast cancer cell cycle and by doing so discovered 2375 proteins. These proteins where then checked for their role in cancer development or as their role as potential biomarkers. It was found that 96 of these proteins were associated with cancer, out of which 51 were specifically involved in breast cancer. A further 57 proteins with a significant relationship to cell cycle regulation and cancer were also found. It was also noted that the majority of the cancer markers included 48 proteins, which were involved in signalling, a table of the proteins involved in the signalling pathways is presented below (table 4). From these results, the paper reported three protein networks were found which included 1) signalling and cell cycle regulation, 2) maintenance of genome integrity and DNA repair and 3) Oxidative phosphorylation, stress, energy production and metabolism. The results also indicated that the majority of cancer marker proteins do not act alone in the development of the disease but rather in networks. It was also found that identified cancer marker clusters contain both agonist and antagonist within the same cluster. Another finding was that the signalling clusters identified can control several cancer related biological processes at once (Tenga and Lazar, 2014).

In addition to the studies (Lindhart, *et al.*, 2016) and Tenga and Lazar (2014), an article written by Dimond (2014), was found which showed the current application of 'omics, this study is still in trial. The trial explores the use of both proteomic and genomic techniques in combination to discuss how they can be used in creating vaccine and drug development for Ebola virus and is currently in phase I, offering much promise. The article identifies the genome of the virus has seven genes these are, 3′ leader, nucleoprotein, virion protein (VP) 35, VP40, glycoprotein (GP), VP30, VP24, RNA-dependent RNA polymerase (L)-5′ trailer (Dimond, 2014).

Transcriptomics

Transcriptomics was only explored in one of the studies found using the search strategy described. This study was carried out by Verbist et al. (2015), who investigated if this specific set of 'omics could be incorporated into early drug discovery in order to prevent late stage failures of drugs. The study found showed the benefits of using transcriptional profiling and high content profiling in the early stage of drug discovery, it showed how it can be used to prevent late failure and thus saving time and cost. 58 compounds where transcriptionally profiled in the drug discovery process in order to find potential signs of polypharmacological effects. The downregulation of tubulin genes were tested as this often suggests genotoxic effects. Compounds, which showed the most downregulation on informative tubulin genes were tested. Following the tests two compounds numbered 8148 and 4782, showed induced large sized micronuclei and an increase in number of bi and polynucleated cells, this suggested spindle poison and aneuploidy. The results were compared to a compound, which did not show tubulin gene downregulation and evidently did show any genotoxic effects. This shows the significance transcriptomics can have on early drug discovery (Verbist, *et al.*, 2015).

Metabolomics

Metabolomics approaches were observed in two of the papers, the first by Armstrong et al. (2014) who explored the role of metabolites in psoriasis and psoriatic arthritis. The study examined 10 psoriasis patients, 10 psoriasis arthritis patients and 10 healthy patients (control), initially the metabolite profiles of the psoriasis and control patients were compared. It those patients who have psoriasis showed an increase in alpha ketoglutaric acid and decreases in asparagine, glutamine and beta-sitosterol in comparison to the control group. After this the metabolite profiles of psoriatic arthritis were then compared to psoriasis patients, the differences where characterised by a decrease in alpha ketoglutaric acid and increases in arabinose, lingoceric acid, phosphoric acid and glycerol-3-galactoside. The study

gives an insight to the benefits of how metabolomics can used to understand the pathophysiology of a disease, thus enabling researchers to offer better therapeutic treatment (Armstrong, *et al.,* 2014).

Metabolomics was also studied in combination with proteomic and genomic approaches in one study, Zhang et al. (2015), where research took place to explore how 'omics data mining can be used in drug repositioning for diabetes. The study found 840 metabolic proteins, 115 genes and 56 proteins associated with diabetes from which 992 diabetic risk proteins were found. Out of the 992 risk proteins a database search indicated 108 of these proteins to be involved in at least one drug project. Using current repositioning theories it was found that a final number of 35 proteins were examined to see if the drugs could be repositioned, the results of the studies indicated that 5 proteins were known drug targets of 22 anti-diabetic drugs already on the market or in clinical trials. The remaining 30 proteins whose current indication was to treat other diseases could be repositioned to treat diabetes; this showed that the current repositioning strategy works well. By comparison, using the 'omics data mining information enabled identification of 58 drugs, which corresponded to the 12 protein targets which had potential therapeutic treatment for diabetes. A table of the 58 drugs which were repurposed using the 'omics method is shown in table 5 (Zhang *et al.,* 2015).

DISCUSSION

With existing drug, development research techniques the time required to develop a drug can take up to 20 years with the cost going into billions of dollars. This review indicated the benefits of applying 'omics to research to reduce not only the time and capital required to develop drugs, but also how 'omics can be exploited in order to find new drug targets, improve drug regimens and bring us closer to personalised medicine. The 12 articles found to be of eligibility all explored different avenues of where 'omics can be applied, examples including drug side effects, cardiovascular disease, type II diabetes, the G1-stage of the breast cancer cycle, Ebola etc. Because of the vast differences in the articles, the results could not be collaborated and a statistical conclusion could not be found, however the findings of this review were clear.

It is clear to say that the most explored 'omics is genomics, this is likely due to previous research in the area such as with The Human Genome Project, which was a study with the aim of being able to determine the sequencing and mapping of all nucleotide base pairs that make up human DNA (National Human Genome Research Institute (NHGRI), 2003). The study enabled researchers to develop a blueprint for building a human being. In addition to this other studies were also conducted which furthered researchers understanding

in this field of 'omics, such as, The 100,000 Genomes Project (Genomics England, 2012). As a result of these projects genomics has therefore been made more easily exploitable for drug development.

The articles found have shown the vast use of genomic profiling in the field of drug development and research. Tremblay and Hamets (2013) study investigated how changes in the genome can lead to a person to becoming susceptible to diseases and also to how the same change could affect how they respond to drug treatment. They concluded that although there are advances being made in the field of personalised medicine, the biggest challenge is bringing the discoveries into clinical care. Simonds et al. (2013) provided further research into the same field and concluded with similar findings, suggesting again that the translation of genomic discoveries into clinical practice is the limiting factor but also added that this was due to insufficient evidence of the benefits in applying genomics over current treatment. However Uzilov et al. (2016), successfully created a personalised cancer therapy program based on genomics, and were able to conclude that overall, the use of the genomics approach was superior to any of the commonly used commercial cancer panel, as by incorporating genomics it was possible to find a significantly greater amount of cancer related somatic mutations and actionable genetic and genomic alterations (Uzilov *et al.,* 2016). Arnaout et al. (2013) constructed a Monte Carlo model to estimate the time and financial costs needed to significantly reduce the rate of drug related adverse outcomes. Their study concluded that using a genomics approach to drug research could save healthcare systems tens of billions of dollars a year and actually reduces drug-related outcomes by up to 50%.

The study carried out by Lefant (2013), also discussed personalised medicine but specifically looked at cardiovascular diseases, the study identified multiple genetic variants associated with cardiovascular disease and some risk factors. The paper found that different ancestries lead to either a loss-of-function or a gain-of-function changed amongst patients, it was specifically found that in Europeans, Africans, and East Asians, the of loss-of-function homozygotes is 15%, 15% and 29% respectively, while the gain-of-function is 21%, 16% and 3% (Lefant, 2013). The study clearly shows the benefits of applying genomics before dictating drug therapy regimens. The final study found which specifically examined genomics was conducted by Wang and Guda (2016), found that genomic profiles for triple negative breast cancer could be used to identify new therapeutic targets or to predict the effectiveness of a targeted treatment strategy. The study found using a genomics profiles (gene expression, gene mutation, methylation and miRNA) it was possible to find hyperactive genes in the cancer, which gave the opportunity to discover potential drug targets, some of which were found to be previously studied whilst others were new. This shows how genomics can offer a more effective approach to finding drug targets over conventional methods.

Proteomics was found to mainly to be involved in finding drug targets and being used as disease biomarkers. Lindhart et al. (2016) constructed a proteomic study to investigate the potential to use proteins to identify normoalbuminuric diabetic patients who progress to overt kidney disease. Although the study is still currently in trial it aims to validate the use of target intervention based on a proteomics-based risk classifier. If validated the biomarker will not only be an earlier marker for diabetic nephropathy, but also a more specific one in comparison to current microalbuminuria tests. Proteomic approaches were also taken by Tenga and Lazar (2014) to identify cancer markers in the G1-stage of the breast cancer cycle, by doing so they were able to conclude that cancer marker regulatory components act within networks rather than alone, this enabled molecular mechanisms of the uncontrolled proliferation of cancer cells and also novel biomarkers and potential drug targets to be identified. Dimond's (2014) study into a vaccine for Ebola further supports the use of proteomics being used to find drug targets after a potential vaccine was made by applying proteomics and genomics to the drug development of the vaccine.

Armstrong et al. (2014), explored how metabolomics could be used to reveal the different pathogeneses of psoriatic diseases. The study was able to show how comparing metabolite differences between psoriasis and psoriatic arthritis can show key differences between the diseases and therefore give a better insight to how therapeutics should be developed in order to tackle each disease successfully. On the contrary Zhang et al. (2015) looked to use the 'omics, in particular metabolomics, find novel indications for drugs already marketed or currently on trial (drug repositioning). The article was able to conclude that incorporating 'omics to repurpose drugs for potential diabetes treatment was successful, as the 'omics data mining method was able to reposition more drugs than current techniques.

The only article found which discussed transcriptomics, looked at how it could be incorporated in the drug discovery process this was conducted by Verbist et al. (2015). After a recent analysis exploring the drug development process it was found that 95% of experimental medicines fail to be both effective and safe. As a result of this, Verbist et al. (2015) explored how transcriptomics could be used to provide a better prediction on toxicology in earlier phases of drug development. It was found that transcriptional profiling can improve the risk/safety assessment in the early stages of drug discovery, in more detail a transcriptional signature was found which was predicative of a genotoxic effect.

The data clearly indicates that each of the 'omics explored are useful to the drug development process in their own way and certain trends were found. An example of this was when conducting the search, it was clear that genomics was the most researched and this is likely due to factors mentioned previously such as earlier treatment in genomics. In addition, to this in terms of how each of the 'omics were incorporated in research it was found that: for transcriptomics it was shown to be useful in the drug discovery process in order to prevent late failures by providing good predictions of toxicology, proteomics on the other hand was

shown to be a valuable tool in order to exploit new potential drug target. Metabolomics was beneficial in understanding the pathogenesis of diseases enabling a better understanding to how the disease could be treated and genomics, although the most studied and with a vast amount of uses, was shown to be the most useful when being applied to personalised medicine or to develop patient specific drug regimens. The biggest disadvantage found was the evidence gap between research and clinical application, this review therefore presents the need for more clinical trials, which incorporating the 'omics, to be conducted in order to overcome this. Nevertheless, the findings from this review suggests the application of 'omics to be a superior method of developing drug over current drug development practices.

In addition to this, the 'omics were not only shown to be effective in drug development from a research point of view but also showed how they could be cost effective. Although the technologies are relatively new and initial use of the 'omics can be expensive, over a period of years they are proven to ultimately save money in comparison to current drug development techniques. This is because firstly using the 'omics in the drug discovery process in order to give a better prediction of which drugs would cause toxicities later on in the development process and therefore saving capital on late failures. Applying the 'omics to drug development research would also give a decrease in adverse drug reactions, this would further increase cost-effectiveness of the process. These factors would not only save billions of pounds' worth of investments, but would also decrease the amount of adverse drug reaction related hospital admissions and save health care providers money too.

Based on the findings of the 'omics examined it is possible that foodomics and lipidomics may also have an insight to offer the drug development industry. Therefore, future examination of literature relating to these areas would be proposed as the next stage for this research. Lipidomics is the study of cellular lipids in biological systems, with each lipid having a unique chemical structure and biophysical properties. With many diseases such as diabetes, obesity and cardiovascular disease involving changes in lipid pathways it is important to consider how this can have an effect on drug action and therefore drug research. 'Striking examples include the discovery of recurrent changes in the phospholipidome of cancer tissues and in sphingolipids in Alzheimer's disease. Combined with transcriptome analysis and other functional genetics tools, these findings have led to new insights in disease mechanisms and to the discovery of potential new targets for drug development' (Dehairs *et al.,* 2015). In the case of foodomics although a smaller and less developed part of 'omics, it is interesting field. Foodomics analyses the effect of food and nutrition, researchers aim to connect foodomics to the health of patients, diseases and drug action (Capozzi and Bordoni, 2012). Unfortunately as this is a relatively new type of 'omics there is little evidence to show its benefits, however it has the potential to provide a novel approaches to medicine and drug development research.

LIMITATIONS

For this review, there are some limitations which should be acknowledged. The first would include that a statistically significant conclusion could not be met, however this was due to the fact that the data extracted from the articles was not comparable. Therefore, a meta-analysis would have been inappropriate for these data sets. In addition to this, the studies included in this review lacked patient participation meaning that there was a lack of clinical trials in this time-frame that could be reviewed. This also meant that it was difficult to test the risk of bias in some of the articles found as they were mainly based on lab research rather than clinical application. Consequently this only enabled a few record found to be assessed using the JADAD scale, as planned. However, it is important to note that although it was difficult to check the risk of bias in all of the articles, the confidence levels were generally well tested meaning that the probability of the results being accurate was therefore also high.

Another limitation of the study included the time-period used for the search criteria as this was restricted to the past four years. This was with the aim to obtain the most recent literature available however, it is clear to say some relevant literature was missed out. Other limitations included that the studies examined were only those in English and only free full text articles or accessible full text articles were used, which also meant more relevant literature may remain unused.

CONCLUSION

There are some key implications that can be drawn from this study. The first being the need for more clinical trials to occur before a meta-analysis and valid statistical conclusion can be reached. As when conducting this study it was found the majority of recent literature based on the field of ‘omics compromised of lab based research rather than patient involvement; however, this is largely down to the current evidence-gap on ‘omics in clinical application.

In addition to this although there is a high potential for transcriptomics and metabolomics in drug development it is clear to say that there is currently a lack of research and studies in this field of ‘omics when comparing to genomics. Therefore, it is highly recommended that further research in such fields should be conducted to test the effectiveness of these ‘omics in drug development research.

Furthermore, this study has clearly been able to implicate the benefits of personalised medicine and showing how ‘omics can be incorporated into this. However, current studies and trials are limited by lack of cost effectiveness over conventional medicine, but with

strong evidence on the benefits of personalised medicine it is another avenue of which drug development research should be heading towards.

Finally, an important impact of this study is the realisation on how ‘omics can be incorporated in order to find new potential drug targets. With drug resistant medication increasing and newer diseases, emerging this clearly shows the potential ‘omics can have of drug development research.

After conducting this systematic literature review and analysing the data and literature extracted, the following conclusion can be made. It is evident that ‘omics technologies are rapidly developing, but further research and trials need to be conducted before we see a merging in to drug development research and in to clinical application. However this review has demonstrated how each of the ‘omics are beneficial in the field of drug development research, showing how a applying the ‘omics can be cost effective, reduce adverse drug reactions, enable researchers to learn more about diseases themselves, find new drug targets and play a vital role in personalised medicine. Overall, the future of drug development seems to lie within the application of ‘omics, but an evidence gap must be fulfilled before this becomes a reality.

REFERENCES

1. Alfirevic, A and Pirmohamed, M (2017) “Genomics of Adverse Drug Reactions.” ***Trends in Pharmacological Sciences*** 38: 100-109.
2. Armstrong, A; Wu, J; Johnson, M; Grapov, D; Azizi, B; Dhillon, J and Fiehn, O (2014) “Metabolomics in psoriatic disease: pilot study reveals metabolite differences in psoriasis and psoriatic arthritis.” ***F1000 Research*** pp: 1-14.
3. Arnaout, R; Buck, T; Roulette, P and Sukhatme, V (2013) “Predicting the Cost and Pace of Pharmacogenomic Advances: An Evidence-Based Study.” ***Clinical Chemistry*** 59: 649-657.
4. Boa, A (2017) “Introduction to Drug Discover.” ***University of Hull***.
5. Bosch, F and Rosich, L (2008) “The Contributions of Paul Ehrlich to Pharmacology: A Tribute on the Occasion of the Centenary of His Nobel Prize.” ***Pharmacology*** 82: 171-179.
6. Capozzi, F and Bordoni, A (2012) “Foodomics: a new comprehensive approach to food and nutrition.” ***Genes & Nutrition*** 8: 1-4.
7. Chong, K (2015) “Warfarin Dosing and VKORC1/CYP2C9.” ***WebMD***: 1-5.
8. Daly, A (2013) “Pharmacogenomics of adverse drug reactions.” ***Genome Medicine*** 5: 1-12.
9. Dehairs, J; Derua, R; Rueda-Rincon, N. and Swinnen, J (2015) “Lipidomics in drug development.” ***Drug Discovery Today: Technologies*** 13: 33-38.

10. Dimond, P (2014) "Omics Find Chinks in Ebola Armor for Vaccine and Drug Development." ***GEN Genetic Engineering & Biotechnology News*** - Biotech from Bench to Business.
11. Elhassa, G and Alfarouk, KO (2015) "Drug Development: Stages of Drug Development. ***Journal of Pharmacovigilance*** 3: 1-3.
12. FDA (2015) "The Drug Development Process."
13. Fdareview.org (2016) "The Drug Development and Approval Process." FDAReview.org.
14. Genomics England (2012) "The 100,000 Genomes Project." ***Genomics England***.
15. Kangelaris, K; Bent, S; Nussbaum, R; Garcia, D. and Tice, J (2009) "Genetic Testing Before Anticoagulation? A Systematic Review of Pharmacogenetic Dosing of Warfarin." ***Journal of General Internal Medicine*** 24: 656-664.
16. Lenfant, C (2013) "Prospects of personalized medicine in cardiovascular diseases." ***Metabolism*** 62: S6-S10.
17. Lindhardt, M; Persson, F; Currie, G; Pontillo, C; Beige, J; Delles, C; von der Leyen, H; Mischak, H; Navis, G; Noutsou, M; Ortiz, A; Ruggenenti, P; Rychlik, I; Spasovski, G. and Rossing, P (2016) "Proteomic Prediction and Renin Angiotensin Aldosterone System Inhibition Prevention of Early Diabetic Nephropathy in Type 2 Diabetic Patients with Normoalbuminuria (PRIORITY): essential study design and rationale of a randomised clinical multicentre trial." ***BMJ Open*** 6: 1-9.
18. Moher, D; Liberati, A; Tetzlaff, J and Altman, DG (2009) "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement." ***The PRISMA Group.***
19. National Human Genome Research Institute (NHGRI) "(2003) "All About The Human Genome Project (HGP)."
20. Simonds, N; Khoury, M; Schully, S; Armstrong, K; Cohn, W; Fenstermacher, D; Ginsburg, G; Goddard, K; Knaus, W; Lyman, G; Ramsey, S; Xu, J and Freedman, A (2013) "Comparative Effectiveness Research in Cancer Genomics and Precision Medicine: Current Landscape and Future Prospects." ***JNCI Journal of the National Cancer Institute*** 105: 929-936.
21. Tenga, M. and Lazar, I (2014) "Proteomic study reveals a functional network of cancer markers in the G1-Stage of the breast cancer cell cycle." ***BMC Cancer*** 14: 1-17.
22. Tremblay, J and Hamet, P (2013) "Role of genomics on the path to personalized medicine." ***Metabolism*** 62: S2-S5.
23. Uzilov, A; Ding, W; Fink, M; Antipin, Y; Brohl, A; Davis, C; Lau, C; Pandya, C; Shah, H; Kasai, Y; Powell, J; Micchelli, M; Castellanos, R; Zhang, Z; Linderman, M; Kinoshita, Y; Zweig, M; Raustad, K; Cheung, K; Castillo, D; Wooten, M; Bourzgui, I; Newman, L; Deikus, G; Mathew, B; Zhu, J; Glicksberg, B; Moe, A; Liao, J; Edelmann, L; Dudley, J; Maki, R; Kasarskis, A; Holcombe, R; Mahajan, M; Hao, K;

Reva, B; Longtine, J; Starcevic, D; Sebra, R; Donovan, M; Li, S; Schadt, E and Chen, R (2016) "Development and clinical application of an integrative genomic approach to personalized cancer therapy." ***Genome Medicine*** 8: 1-20.

24. Verbist, B; Verheyen, G; Vervoort, L; Crabbe, M; Beerens, D; Bosmans, C; Jaensch, S; Osselaer, S; Talloen, W; Van den Wyngaert, I; Van Hecke, G; Wuyts, D; Van Goethem, F. and Göhlmann, H (2015) "Integrating High-Dimensional Transcriptomics and Image Analysis Tools into Early Safety Screening: Proof of Concept for a New Early Drug Development Strategy." ***Chemical Research in Toxicology*** 28: 1914-1925.
25. Wang, X and Guda, C (2016) "Integrative exploration of genomic profiles for triple negative breast cancer identifies potential drug targets." ***Medicine*** 95: 1-12.
26. Zhang, M; Luo, H; Xi, Z. and Rogaeva, E (2015) "Drug Repositioning for Diabetes Based on 'Omics' Data Mining." ***PLOS ONE***, 10: 1-13.

Correspondence Author:

Craig Allan Russell

Aston School of Pharmacy, Aston University, Birmingham, UK. B4 7ET

Phone: 0121 204 3077

Email: c.russell6@aston.ac.uk

Cite This Article: Chowlia, BS and Russell, CA (2017), "A Systematic review examining how 'omics are applied to drug development research." ***International Journal of Drug Research and Technology*** Vol. 7 (4), 162-179.

INTERNATIONAL JOURNAL OF DRUG RESEARCH AND TECHNOLOGY