IMAGE INFORMATICS APPROACHES TO ADVANCE CANCER DRUG DISCOVERY

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DECLARATION

This thesis presents my own work, and has not been submitted for any other degree or professional qualification. Wherever results were obtained in collaboration with others, I have clearly stated it in the text. Any information derived from the published work of others has been cited in the text, and a complete list of references can be found in the bibliography. Published papers arising from the work described in this thesis can be found in the appendices.

– Scott Warchal, 2018

epigraph here

ACKNOWLEDGEMENTS

Acknowledgements here.

ABSTRACT

Abstract here.

LAY SUMMARY

Lay summary here.

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LIST OF FIGURES

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LIST OF ACRONYMS

2D Two-dimensional

3D Three-dimensional

CNN Convolutional neural networks

DMSO Dimethyl sulfoxide

FDA U.S Food and Drug Administration

HTS High throughput screening

MOA Mechanism of action

PBS Phosphate buffered saline

PCA Principal component analysis

PDD Phenotypic drug discovery

TCCS Theta comparative cell scoring

1 INTRODUCTION

1.1 Eroom's Law: The increasing cost of drug discovery

Throughout the last 70 years the cost of developing a new drug has steadily increased. Scannel *et al.* observed that the cost to develop a new drug has approximately doubled every 9 years[1]. This observation has been dubbed "Eroom's law", a homage to Moore's law – a well-known observation that the number of transistors in microprocessors approximately doubles every 2 years. The cost of bringing a new drug to market is now approaching £1 billion, taking 10 years from initial concept to approval, the reasons behind this every-increasing cost are multi-faceted. One explanation may be that the low-hanging fruit has been taken, effective long-standing remedies have been studied and commercialised, natural products screened, and we are now tackling the more complex diseases and pharmacological targets.

1.2 The Drug Discovery Process

`TODO:` A brief section on the drug discovery process, hit -> lead -> validation -> clinical trials -> approval.

1.2.1 Target-Based Screening

Over the past 30 years the majority of drug discovery programmes seized upon new advances in robotics and automation to screen ever-expanding compound libraries against hypothesised protein targets. It would be difficult to argue that this target-based high-throughput screening (HTS) approach has not been fruitful, and has yielded many succesful therapeutics. Despite HTS's clinical and commerical success stories, it is not a panacea, with a high attrition rate of candidate compounds once they enter clinical trials. A large proportion of clinical trial failures are due to a lack of efficacy (`TODO:` get value), which can usually be traced back to an incomplete understanding of disease aetiology.

1.2.2 Phenotypic Screening

1.3 High content imaging

1.4 Cancer

2 CELL MORPHOLOGY CAN BE USED TO PREDICT COMPOUND MECHANISM OF ACTION

2.1 Section name

Stuff here, text text text test citation[2].

3 | MEASURING DISTINCT PHENOTYPIC RESPONSE

3.1 Section name

4 LARGE COMPOUND SCREEN ACROSS 8 BREAST CANCER CELL LINES

4.1 Section name

5 CHEMINFORMATICS

5.1 Section name

6 DISCUSSION AND CONCLUSION

6.1 Section name

BIBLIOGRAPHY

[1] Jack W Scannell, Alex Blanckley, Helen Boldon, and Brian Warrington. "Diagnosing the decline in pharmaceutical R&D efficiency". *Nature Reviews Drug Discovery* 11.March (2012), pp. 191–200.

[2] Mi Yang, Jaak Simm, Pooya Zakeri, Yves Moreau, and Julio Saez-Rodriguez. "Linking drug target and pathway activation for effective precision therapy using multi-task learning". *bioRxiv* (2018), p. 225573.