

**DEVELOPMENT OF NOVEL  
THERAPIES FOR GUT DYSBIOSES**

**A Thesis Submitted For the Degree  
Of Doctor of Science**

**By**

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**2016**

## DECLARATION

I certify that the work in this thesis has not previously been submitted as part of requirements for a higher degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me.

Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

Signature of Student: \_\_\_\_\_

Date: \_\_\_\_\_

*11 July 2016*

## ACKNOWLEDGEMENTS

The work that led to this Thesis was carried out over 30 years at the Centre for Digestive Diseases starting with the establishment of the clinic on 16th October, 1984 and was completed in early 2015. The work was carried out during routine clinical sessions, after hours, often on weekends, on international travel where writing was so much easier, but in particular during stimulating sessions with numerous staff members, Researchers, Research Managers of the clinic and in particular, Professor Robert Clancy – Professor of Pathology, Faculty of Health and Biomedical Sciences, University of Newcastle. I am indeed grateful to Professor Clancy for his invaluable support, guidance, ideas and help with the construction of the writing. I'd also like to thank Professor Ian Charles, the head of i3 Institute for his help and support in progressing the work through discussion session.

I would like to give my special thanks to my parents Danuta and John Borody who taught me to catch the vision of the future and then supported me through times of hardship when that future wasn't arriving quickly enough. They did teach me patience and perseverance which was so crucial to the completion of the work over the thirty years.

My thanks are also due to the large number of people who have provided me with assistance, technical help and support including Dr Gerald Pang, then of the discipline on Immunology and Microbiology, Faculty of Health and Biomedical Sciences, University of NSW. I'd like to thank also Professor Hazel Mitchell and Dr Stewart Hazel for their help with the Helicobacter work over those years especially in culture and sensitivity training. At the Centre for Digestive Diseases, the Research department had numerous managers and members over the years. Each of these people contributed to the work described in the Thesis and some can be seen as co-authors in the many papers that eventuated. These people include Rosa Surace, Nicholas Shortis, Margaux Alvaran, Kylie Herdman, Sarah Finlayson and Anthony Jaworski.

Of the clinical team there were numerous people who have helped but in particular those who have been with me here for more than 21 years include Sister Sharyn Leis who has expertly administered the entire FMT program and donors. She is perhaps the most experienced FMT nurse in the world. Along with Sharyn and with me for more than 21 years is the technical nurse that ran the endoscopy segment of the CDD – Sister Soledad Monzon. Many other nursing staff in the CDD Clinic have helped daily in managing patients who formed the basis of the research work carried out here. Most of this work could not have been done without the procedural aspect of this work, and those who expertly sedated the numerous patients involved in clinical research. These include Drs Sanjay Ramrakha, John Saxon, Andrew Finch and Anis Yusuf. Without them we would not have been able to collect specimens and biopsies from the patients who underwent various research projects. I would also like to thank the Gastroenterologists in this practice who contributed with their clinical expertise and their patients during recruitment for various trials. These include Dr Antony Wettstein, Dr Simon Benstock, Dr Suhidran Vivekanadarajah, and Dr Gaurav Agrawal. Other members of the Research department of the CDD also contributed greatly in writing research protocols submitting them to the Ethics Committee and organising the recruitment of patients for the trials.

I wish also to acknowledge the help and support in the editing and creating of the thesis, especially Miss Jordana Campbell and my Personal Assistant, Carmen Schwarz, both of whom are experts in their respective fields, and Scott Mitchell from the Research department accurately compiling the Thesis.

Finally, I'd like to acknowledge my patient partner, Vic Dawson for encouraging me keep going and to get through the work, much of which was done after hours well into the night where we could not be home together.

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## ABSTRACT

This thesis reports results of 30 years of systematic clinical investigations carried out by the author in the general area of “*infection-driven inflammation*”. The Centre for Digestive Diseases (CDD) endoscopy clinic was founded by the author in 1984 closely coinciding with Drs Barry Marshall and Robin Warren reporting gastric spiral bacteria with pathogenic role in ulcer disease. CDD was able to source gastric biopsies with *Helicobacter pylori*(HP) from numerous patients with ulcer disease creating the environment necessary for HP research. Hence, *Section 1* of the Thesis describes systematic studies which asked questions such as ‘which is the best therapy’, ‘what is the role of acid suppression’ and the ‘role of cigarettes’? This culminated in the development of ‘*triple therapy*’, the first clinically effective HP cure commercialised later as *Helidac*.

Success in HP research soon led to the treatment of the candidate infective cause of Crohn’s disease called *Mycobacterium avium subspecies paratuberculosis* (MAP). This comprised of three antibiotics which were active intracellularly - another ‘triple therapy’ akin to HP treatment. However, curing HP could be achieved in 7 days and ulcer healing in 6 weeks whereas MAP – one of the slowest growing bacterial pathogens – required treatment for many months to heal the bowel. So in *Section 2* of the Thesis the effect of Anti-MAP therapy on healing Crohn’s disease was studied. Funding from the Broad Foundation supported culture and PCR of MAP while an Israeli company, RedHill Biopharma has funded current pivotal trials with a view to an FDA approval.

*Section 3* of the Thesis describes research in Faecal Microbiota Transplantation (FMT). FMT was first used at CDD in 1988 in a patient with indeterminate colitis - the first patient world-wide treated for colitis and cured. Generally *Clostridium difficile* infection (CDI) is treated with FMT at CDD with a cure rate exceeding 95%. Subsequently over 6,000 FMT treatments were carried out and new indications for FMT were discovered, both within and outside of the GI tract. These included ulcerative colitis, irritable bowel syndrome, constipation, MS, arthritis, acne, and others, reported in enclosed publications. CDD work in FMT contributed to the global growth of microbiome research and culminated in the creation of the lyophilised encapsulated FMT.

Each of the three Sections has addressed “*infection-driven inflammation*” in different body regions. It is hoped that reported findings in this Thesis will lead to new therapies that will result in significant clinical improvements.