3rd College of Physicians' Lecture – Translational Research: From Bench to Bedside and From Bedside to Bench; Incorporating a Clinical Research Journey in IgA Nephritis (1976 to 2006)†

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Abstract

Translational research (TR) can be defined as research where a discovery made in the laboratory (bench) can be applied in the diagnosis, treatment or prevention of a disease. Examples of medical discoveries contributing to translational medicine (TM) include the isolation of insulin by Banting (Nobel Laureate, 1923), the discovery of penicillin by Alexander Fleming (Nobel Laureate, 1945) and recently the discovery of the role of bacterium *Helicobacter pylori* in the causation of gastritis and peptic ulcer by Marshall and Warren (Nobel Laureates, 2005). Clinical research (CR) would be a more appropriate term for the bulk of research work undertaken by doctors. CR embraces both clinical based and laboratory-based research. The terminology "bedside to bench" applies more to CR as opposed to "bench to bedside" in the case of TR. But regardless of who does it, as long as the discovery can be translated to the bedside and results in improvement in patient care it can be considered a contribution to TM. Our work spans a 30-year period, involving laboratory-based research, clinical trials and genomics of IgA nephritis (Nx). This is a series of work to elucidate the pathogensis and therapy of IgANx. Plasma beta-thromboglobulin (BTG) an in-vivo index of platelet aggregation and anti-thrombin III increase due to a constant thrombogenecity resulting from platelet degranulation formed the basis for anti-platelet and low-dose warfarin therapy. A study of the natural history of IgANx revealed 2 courses, a slowly progressive course with end-stage renal failure (ESRF) at 7.7 years and a more rapid course at 3.3 years. Triple therapy (cyclophosphamide, persantin and low-dose warfarin) delayed progression to ESRF by about 8 years and for some patients up to 20 years. Documentation of abnormal suppressor T cell function provided the basis for immune therapy. Four patterns of proteinuria were present in IgANx and it is the quality and not so much the quantity of proteinuria which determined the prognosis. Low molecular weight proteinuria was a bad prognostic marker. A controlled therapeutic trial using ACEI/ATRA showed that therapy decreases proteinuria, improves renal function and converts non-selective to selective proteinuria. Subsequent work confirmed that it was the ATRA, not the ACEI which contributed to improved renal function. Individual anti proteinuria response to ATRA varies depending on ACE gene polymorphism. We found that the II genotype of the ACE gene was renoprotective and patients with this genotype had significantly reduced incidence of ESRF compared to those with the DD genotype. Patients responsive to ATRA therapy can retard progression to ESRF by up to 32 years. Mild renal failure can be reversed with possible regression of glomerulosclerosis because of glomerular remodelling by ATRA.

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Introduction

In our quest to pursue knowledge regarding a patient's illness or seek a cure for the disease, as doctors we have to derive the necessary answers through physical examination of the patient and investigations either at the bedside or the laboratory. We engage in research activities into the patient's illness so that we can alleviate his suffering and eradicate the disease. The knowledge gained from such research

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activities if translated into procedures or remedies, which can improve the patient's medical condition, contribute to what is known today as translational medicine (TM). But TM is really nothing new. The early physicians have practised it for ages.

I. TM and Research

Translational research (TR) can be defined as research where a discovery made in the laboratory (bench) can be applied in the diagnosis, treatment or prevention of a disease. In a broader definition, TR can refer to any form of research, which embraces new technological or biomedical advances including clinical trials (both drug and non drug) which contribute to an improvement in patient care in the clinical setting.

There is an elite group of medical researchers known as clinician scientists who are best positioned to do work involving TR or TM. Basically, these researchers are trained clinicians who are also trained researchers. But because of their medical training they would be best poised to ask the critical research question to formulate the research hypothesis needed to address a particular problem which they encounter in clinical practice. The research question therefore could be a basic research question pertinent to a particular disease or it could be a clinical question raised at the patient's bedside, which seeks a research solution from the laboratory (bench). Hence, the terminology in TR, from bench to bedside and bedside to bench.

What about basic research or clinical research done by the scientist or the clinician? Both the scientist and clinician can do basic research so long as they have received the necessary training in bench work. Whilst the current medical research focus is on TR, one must remember that current TR is built on the foundations of fundamental basic research. The difference is that much of basic medical research is often undirected and has no immediate clinical impact. However, supporting basic research is important since we cannot predict which of today's extraordinary ideas in basic science will lead to clinical applications in the future.[1]

Apart from TR and basic research, much of the research work undertaken by doctors today would be considered clinical research which can be further classified into purely clinical (non-laboratory) based research and laboratory-based research. Clinical (non-laboratory) based research could involve incidence studies of diseases, epidemiology, clinical trials (drug and non-drug), natural history of diseases and documentation of interesting case reports or successful therapy.

Laboratory-based clinical research refers to research conducted in the laboratory using patient material (blood, body fluids, tissue samples) to find answers or solutions to clinical questions raised at the patient's bedside. Hence, the terminology "from bedside to bench" would seem more appropriate as opposed to "bench to bedside" in the case of TR.

But, regardless of the type of research, whether it is basic research, TR or clinical research, as long as the discovery can be translated to the bedside and results in improvement in patient care it is considered a contribution to TM.

II. Historical Perspectives of Medical Discoveries That Contributed to TM

There are many interesting stories about how medical history was made through the famous discoveries of medical giants and these discoveries have helped to save millions of lives through the ages. These are products of great scientific minds in the field of medicine.

The discovery of penicillin in 1928 by Alexander Fleming[2] remains as one of the milestones of medical therapy. Fleming had observed that colonies of bacteria *Staphylococcus aureus* could be destroyed by the mold *Penicillin notatum*. It struck him that an antibacterial agent must be causing this phenomenon. His discovery led to the principle that medicine could kill bacteria inside the body. It was only in the early 1940s that Howard Florey and Ernst Chain could isolate the active ingredient and developed the powdery form of the medicine. In 1948, Andrew Moyer was granted the patent for mass production. This is a classic story of TM.

The Salvarsan Story is no less exciting. In 1910, Paul Ehrlich introduced an arsenic-based drug Salvarsan to treat syphilis, a public health scourge like HIV today. His methodical search for a specific drug to treat specific diseases marked the beginning of targetted chemotherapy. As a medical student, Ehrlich was fascinated by aniline (a new synthetic dye) which could stain specific microbes. He predicted that chemists could create "magic bullets" targetted at a parasite. He took aim at syphilis, an incurable disease in those days due to *Treponema pallidum*.

Ehrlich assembled a multidisciplinary team of scientists including chemist Alfred Bertheim and bacteriologist Sahachiro Hata. They chose an organic arsenic compound and synthesised hundreds of related organo arsenic compounds. Each compound was tested for biologic activity, toxicity and distribution in syphilitic rabbits. Number 606 (Salvarsan) was proven efficacious. A single dose of 606 cured the rabbit. It was discovered in the fall of 1909 and was used in clinics by 1910, a speed unheard of in this day and age.

Hoechst manufactured Salvarsan. It became the most widely prescribed drug in the world. It was the world's first blockbuster drug. It remained most effective for syphilis until penicillin became available in the 1940s. Salvarsan's success represented the promise of modern medicine. It

meant that effective synthetic drugs could be devised to treat disease, truly another great classic in TM.

Ignaz Semmelweis (1818-1865) is no less another giant in TM. In those days, 12 out of 100 Hungarian women who gave birth died from childbirth fever. A doctor, at that time, would go straight from an autopsy, where he was cutting up a corpse riddled with disease, to the bedside of a woman in labour. With the same hands that had recently been covered with putrid bodily fluids, he would probe around or inside the woman's body in the course of delivering the baby.

At that time, there were many maternity hospitals in Budapest where the mortality rate from childbirth fever approached 100%. For that reason, women who had the means would rather have their babies delivered at home. Semmelweis had discovered that a simple procedure like hand washing with carbolic soap could prevent the occurrence of childbirth fever in his patient. When he reported this finding, the reaction of the medical community at that time was one of ridicule. He was subjected to mockery and persecution which became so severe that, overcome with depression, he took his own life while in a mental asylum.

The very same year that Semmelweis died, Joseph Lister, the discoverer of antiseptic medicine, performed the first germ-free operation. At that time, even the smallest surgical procedure carried a 50% risk of death. This was not due to the surgery itself, but to the inevitable infection transmitted by unsterile instruments and unwashed hands. Lister's innovations were stunning. Those patients expected to die did not die. Again, persecution became Lister's immediate reward. His discovery, and his theory that germs caused wounds to become infected, earned him immediate scathing and constant denouncements from the day's top medical authorities.

But Lister was made of sterner stuff. He had remarkable perseverance and self-sacrifice. He continued striving in the face of incredible discouragements. Eventually, he proved to everybody's satisfaction that both he and Semmelweis were correct, but only after tens of thousands had died through their doctors' refusal to examine the evidence themselves. Semmelweis and Lister, through their innovative contributions of hand washing and sterilisation of medical instruments helped saved countless patients who would have otherwise died.

The Chinese Emperor Shen Nung, born 3000 BC, tested medical herbs. He ate 365 types until he turned green and died from toxic overdose. His medical knowledge, preserved by his court, was handed down to generations of Chinese doctors. His first remedy was *Cannabis indicia*, which was also recorded in Homeopathic Materia Medica.

A famous physician, Hua Tuo[3] (Born 110 AD, died 207 AD) of the Han Dynasty had his name and image adorning numerous medical products (acupuncture needles, medicated plasters). He founded herbal anaesthetics, *Mafai San*, a numbing powder. He was the first surgeon in China and was personal physician to Cao Cao (Romance of the Three Kingdoms). He was sentenced to death when he suggested treating Cao Cao's headache with brain surgery (suspected assassination attempt).

The tradition of testing remedies, what we may consider clinical trials today, was also alive in the ayurvedic tradition held by the Sandhus of India. These sects ate the plants to experience their action on the human body.

III. Our Clinical Research Journey in IgA Nephritis (1976-2006)

In this paper, most of the work we present would focus on IgA nephritis (IgANx) which is the commonest form of glomerulonephritis (GN) occurring worldwide and in Singapore as well. This work spans almost 30 years or 3 decades involving laboratory-based research, clinical trials and in the later part, genomics of IgANx.

Professor Chan Soh Har, Director of the WHO Immunology Laboratory then based in MacAlister Road was my first research teacher (1976). One of the early projects we undertook was to address the question of whether the uremic factor was in the serum or the cell (lymphocyte). In the paper "*The Mixed Lymphocyte Reaction (MLR) and the Response to Phyto-hemagglutinin in Patients with Renal Failure*", we reported that cell mediated immunity was impaired in patients which chronic renal failure and that the MLR in renal allograft recipients could serve as a sensitive monitor of the dose of immunosuppressant.[4]

After a 6-month attachment at the WHO laboratory with hands on laboratory exposure (protected time for research from my kind boss Dr Lim Cheng Hong), I spent a year at the Royal Melbourne Hospital with Professor Priscilla Kincaid Smith on a Colombo Plan Fellowship for a Clinical and Research attachment. At that time, Professor Kincaid-Smith's focus was on the role of platelets in glomerulonephritis. She had devised a combination therapy of cyclophosphamide, persantin and warfarin (CPW) known as the Melbourne Cocktail, which she utilised in the treatment of many patients with various forms of glomerulonephritis with good results. My task was to look for platelet involvement in glomerulonephritis to support the role of persantin in the Melbourne Cocktail. Together with Professor Judith Whitworth (my Research Mentor), we found supporting evidence for platelet involvement through the circulating platelet aggregate ratio (CPAR) and elevation of plasma beta thromboglobulin, an in-vivo index of platelet aggregation in patients with membranoproliferative GN

and focal sclerosing GN.[5]

Back in Singapore in 1979 we were faced with the task of treating patients with IgANx. We asked the following questions: Are platelets and thrombogenecity involved in IgANx? What is the natural history of IgANx? How do we treat this disease, which was the commonest cause of kidney failure in Singapore then? We started several projects at almost the same time. We studied the natural history of IgANx. We embarked on a controlled clinical trial using a modified CPW regimen. And we looked for laboratory evidence of platelet involvement (beta thromboglobulin or BTG) and thrombogenecity (anti-thrombin III or AT III) in IgA nephritis. Our studies showed that plasma BTG was elevated in IgA nephritis and was correlated with the degree of glomerular sclerosis and could form a basis for anti-platelet therapy.[6] We also found that anti-thrombin III was also elevated in IgANx due to a constant thrombogenic tendency as well as increased platelet aggregation and degranulation with release of AT III from platelets. The increased levels were correlated with proteinuria, glomerular sclerosis and crescents on biopsy, suggesting that low-dose warfarin therapy could be useful.[7]

Meanwhile, our study of the natural history of IgANx involving 151 patients followed up for 50 ± 34 months had shown that the patients had 2 clinical courses, one was a slowly progressive course with end-stage renal failure (ESRF) at 7.7 years, while the other a more rapid course with ESRF within 3.3 years. The poor prognostic indices were proteinuria >1 gm a day, hypertension and presence of crescents on renal biopsy.[8]

Our paper on the effects of a 3-year triple therapy (modified CPW) in IgANx was published in 1987,[9] which reported a control trial of 104 patients. The entry criteria depended on renal function, degree of glomerular sclerosis and proteinuria. Those in the treatment group had delayed progression to ESRF by about 8 years and for some patients up to 20 years. This trial subsequently using only persantin and low-dose warfarin was repeated successfully by Lee et al[10] in 1989. Today, this therapy is classified as level 1 evidence supporting a grade A recommendation for treatment of IgANX.[11] The evidence base for the therapy was provided from further work by Lee et al[12] and Liem et al[13] from their work on mesangial cells and umbilical cord endothetial cells. Both showed the effects of persantin and warfarin on the suppression of cell proliferation through cytokine (PDGF) inhibition.

Further work in the WHO Immunology Laboratory with Professor Chan Soh Har showed that patients with IgANx have abnormal suppressor T cell function.[14] This paper was accepted for oral presentation at the International Society of Nephrology Meeting in Greece (1980). It was at this historic meeting that I met my 3 IgA friends – Hideto Sakai, Yasuhiko Tomino and Endoh. We were to share information on our work on IgANx over the next 2 decades. Our immunological studies provided the basis for the use of steroids and cyclophosphamide.

In 1987, our work in IgANx was formally recognised and we were invited to the International IgANX club where we presented our work in Bari, Italy in 1987.[15] Our papers were published, students and visitors came to visit our centre and we were invited to present our work at various scientific meetings. In 1996, Singapore hosted the 7th International Symposium on IgANx.

The study of proteinuria formed another significant aspect of our work in IgANx. We had reported the pattern and behaviour of proteinuria in IgANx through our papers on protein selectivity,[16] SDS-PAGE[17] and iso-electric focussing.[18] We had documented 4 patterns of proteinuria in IgANx and produced data to confirm that it is not the quantity but also the quality of proteinuria in IgANx which determined progression and prognosis in IgANx. We also documented low molecular weight (LMW) proteinuria as a bad prognostic marker.[17] This is now widely accepted.

At the turn of the century (2000) we published our paper "*ACEI/ATRA Therapy Decreases Proteinuria by Improving Glomerular Permselectivity in IgANX*".[19] This was a controlled therapeutic trial in IgANX which showed that the therapy decreases proteinuria, improves renal function and converts non-selective to selective proteinuria. We showed that 8/21 (38%) patients had improved renal function, with 3 of them who had mild renal failure normalising renal function. Hitherto the use of ACEI/ATRA was only aimed at protein reduction with a view to retard progression of renal function. But here we had reported that therapy could not only improve renal function but also restore normal renal function among those patients with mild renal failure. Subsequently, from our further work, we showed that it was the ATRA and not the ACEI which contributed to improved renal function.[20] The present evidence now supports that ATRA causes amelioration of renal lesions and remodelling of renal architecture by reducing TGF beta production in the glomerulus, thus decreasing mesangial cell proliferation and sclerosis.[21] This form of therapy offers a new outlook compared to our earlier therapy with CPW which only aimed at retarding the progression of renal failure. Using supernormal doses of ATRA therapy, we are geared towards restoration of normal renal function in patients with mild renal impairment.[22] ATRA therapy can remodel the damaged glomerular cell with eventual regression of glomerulosclerosis.

One of the questions we sought answers to was why some patients with IgANX respond to therapy with ATRA and others do not? Our hypothesis was that individual antiproteinuric response to ATRA therapy varies depending

on ACE gene polymorphism. Vleming et al[23] and Yoshida et al[24] had postulated that those with the D allele of ACE gene polymorphism respond better to the antiproteinuria effect of ACEI therapy.

We therefore decided that we had to embrace the new science of genomics to look for our solutions to our patients' problems. In 2002, we published "*IgA Nephropathy: Effects of Clinical Indices, ACEI/ATRA Therapy and ACE Polymorphism on Disease Progression*".[25] In a study of 118 Chinese patients with IgANX and 94 healthy Chinese subjects, we found that (i) ACE DD genotype was associated with IgANX and (ii) DD genotype was associated with progression to ESRF.[25,26]

IV. Disease Progression and the Influence of Genomics in IgA Nephritis

Rare inheritable diseases such as cystic fibrosis are caused by single gene defects that may be traced through genetic linkage analysis in affected families. However, for common diseases such as diabetes, hypertension and IgA nephritis, it is likely that multiple genes may be involved, each contributing a small effect to the pathogenesis.[27] Furthermore, environmental conditions and stress may also play important roles in the activation and maintainence of defective gene expressions. Hence, it is much harder to locate these genes and to delineate their contribution to the risk of common diseases. Nevertheless, with the advent of microarray technology of extremely high through-put and coupled with computer-empowered bioinformatics to handle the vast amount of data that are generated, the present is an exciting time for elucidating the causes and pathogenesis of these diseases.[28-30]

(i) Role of ID Polymorphism of the ACE Gene

Human genetic studies revealed that all genes comprising the renin-angiotensin system (RAS) have several forms of polymorphism; raising the possibility that activity of RAS may vary among individuals according to their genetic make-up. One such polymorphism is the deletion/insertion (I/D) polymorphism of the ACE gene. Individual anti-proteinuric response to ACEI/ATRA therapy varies depending on ACE gene polymorphism.[23,24] In this controlled trial, patients were followed up for 5 years to determine their long-term renal outcome to ACEI/ATRA therapy and to ascertain if their ACE gene profile (ID polymorphism) could play a role in determining their response to therapy.

Seventy-five patients with biopsy proven primary IgANX entered a 5-year controlled trial, with 37 in the treatment and 38 in the control group during the period from October 1999 to December 2000. Their ACE gene ID genotypes were studied in order to compare the effects of ID polymorphism on the response to ACEI/ATRA therapy. In the control group, hypertension was treated with atenolol, propranolol, hydrallazine or methyldopa. The patients in the treatment group were treated with ACEI/ATRA therapy or both and reviewed at 3 monthly intervals. Patients were initially prescribed 5 mg enalapril (ACEI) or 50 mg losartan (ATRA) which was increased to 10 mg or 100 mg, respectively, if proteinuria had not decreased to less than 1 gm a day.

Genomic DNA was extracted from peripheral leukocytes and PCR amplification of the DNA sequence containing the polymorphism was performed using sense and anti-sense primers. DNA fragments were then separated and viewed on 2% agarose ethidium bromide gel. Genotypes were identified by the absence or presence of DNA fragment obtained. There are 3 ACE genotypes: DD, II and ID.

The post trial serum creatinine in the control group was significantly worse than the treatment group (5.0 ± 2.8 mg/dL versus 2.4 ± 2.0 mg/dL, $P < 0.001$). The post-trial proteinuria in the control group was also worse than in the treatment group (1.9 ± 1.0 gm/day versus 1.1 ± 0.9 gm/day, $P < 0.002$). With regard to renal outcome, there were 21 patients with ESRF in the control group compared to only 7 in the treatment group ($\chi^2 = 5.4$, $P < 0.005$). Treatment does seem to reduce the number of patients progressing to ESRF. For those with II genotype, there were significantly fewer patients with ESRF in the treatment group when compared to the control group ($P < 0.02$). For those with the ID and the DD genotype, there was no significance in the renal outcome between the treatment and control group.

Contrary to what earlier workers have postulated, that patients with the ACE gene respond best to ACEI therapy,[23] our data have shown that indeed those with the D allele do poorly, have a higher incidence of ESRF and progress to ESRF much faster compared to those with the II genotype. We conclude that ACEI/ATRA therapy was effective in retarding disease progression in IgANX. However, treatment significantly reduced the incidence of ESRF only in patients with the II genotype but not in those with ID or DD genotype.

(ii) Analysis of Genome-wide Gene Expressions in IgA Nephropathy

DNA microarray technique allows tens of thousands of gene expressions to be examined all at the same time. Now, commercial availability of microarray genechips has made this powerful tool more accessible for wider utilisation in the study of diseases. We had screened 7 patients with IgA nephropathy and 7 normal healthy subjects for the differential expression of genes, genome-wide. Leukocyte RNA isolates were purified with DNase to remove contaminating DNA. The Human Genome U133 Plus 2.0

Arrays (Affymetrix, USA) were used to quantitate the differential expression of 38,500 well-characterised human genes. A total of 7761 gene expressions were identified that have an IgAN/normal gene expression ratio of 0.06 fold to 5.58 fold. About 35% of the altered gene expressions have no gene title or just a hypothetical protein label such as FLJ30679. Most of the remaining 65% are identified proteins but whose importance to IgAN is not immediately apparent. Among the 30 most upregulated and 30 most downregulated genes are urotensin 2 (upregulated 3.09-fold, $P < 0.05$) and fatty-acid binding protein 6 (down-regulated to 0.12-fold, $P < 0.05$). Retinoic acid receptor alpha (vitamin A receptor) was found downregulated to 0.41 fold ($P < 0.005$). Preliminary analysis has implicated urotensin 2, disturbance in lipid metabolism and vitamin A deficiency in the pathogenesis of IgA nephropathy. These are relevant new targets for further research and development of new drug therapy. Microarray technology is a powerful tool for discovering and understanding the molecular mechanism in IgAN and other diseases.

(iii) Screening for Susceptibility Genes in IgA Nephropathy

IgA nephropathy (IgAN) is a complex disease, which may be triggered by environmental factors such as an unhealthy "heaty" diet in a genetically susceptible individual. Commercial availability of high-density microarray for parallel genotyping >10,000 single nucleotide polymorphisms (SNPs) has made easy genome-wide screening for disease associated genetic variants. Using the GeneChip Human Mapping 10K Array Xba 142 2.0 (Affymetrix), we performed whole-genome scans in 12 IgAN patients and 8 healthy subjects. Automated genotype calling rate achieved 97.1% overall in 10,204 SNPs. Significant difference in allele counts between patients and controls were observed in 111 SNPs with $\chi^2 > 6.6$ and < 0.01 P values. Annotation from Affymetrix analysis centre mapped only 29 of these to the intron of specific transcripts, directly implicating the encoded proteins. These include known, hypothetical or unknown proteins that fall in the gaps in the genome coverage. About half of the identified gene products (14/29) are membrane proteins. There are multiple functions and interactions among the proteins. The result is a web of regulatory mechanisms and signalling pathways. Their involvement in IgAN is not readily apparent from this mass of information. More work is needed to identify the relevant linkages. Affymetrix GeneChip 10K mapping focuses on 29 SNPs with significant difference in allele counts between IgAN patients and healthy controls. This helps to focus our research efforts and set priority proteins for immediate study, thus minimising efforts while maximising results. However, appreciation of the results remains difficult amidst the tangled pathways and multiple interactions and numerous regulatory roles that many proteins have with one another. With greater than 10 million SNPs genomewide to explore, more work is needed to identify the mechanisms and susceptible genes in the pathogenesis of IgAN.

Conclusion

In this lecture we have espoused a philosophy for TM. We have also shared with you our clinical research journey in IgA Nx to illustrate various aspects of medical research. With the advent of proteomics and genomics, a different world beckons researchers. Truly we are poised on the threshold of an era with many promises for medical breakthroughs which will translate into a better tomorrow for our patients.

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