

# The Quest for Innovative Science

By Prof Ariff Bongso

## Copyright credit line:

Reprinted (abstracted/excerpted) with permission from Bongso, A. (2002) *The Quest for Innovative Science*. Next Wave: <http://nextwave.sciencemag.org/sg>. Copyright 2002 American Association for the Advancement of Science.

In "The Quest for Innovative Science," eminent *in vitro* fertilization (IVF) specialist and founder scientist of Embryonic Stem Cell International (ESI), Professor Ariff Bongso, shares the story of his scientific endeavors. These include several "firsts" and the establishment of ESI, which aims to become the world leading provider of products and technologies derived from human embryonic stem cells. Bongso has authored 410 publications in refereed journals, including the paper "Embryonic Stem Cell Lines from Human Blastocysts: Somatic Differentiation *in vitro*" in *Nature Biotechnology*, 18, pp. 399-404 (2000), and chapters in books. He also holds patents on the "Isolation and development of human embryonic stem cell lines" (1999) and "Derivation and propagation of embryonic stem cells on human feeders and feeder-free matrices" (2001).

## STARTING FROM VETERINARY MEDICINE

Born in Colombo, Sri Lanka, I had my basic education at the prestigious Royal College, Colombo, a public school established by the Queen of England, which to date remains Sri Lanka's leading premier school. Following my GCE 'A' Levels at the Royal College in 1966, I was offered an undergraduate course in human medicine, but for several reasons, I chose to undertake veterinary medicine instead. First, I knew that the 5-year veterinary medicine program would be more intensive than human medicine because the health and husbandry of a variety of agricultural and companion animals had to be studied. Moreover, the fact that my patients would not be able to speak would make it more challenging to make a diagnosis and offer treatment. Second, animal biotechnology was given pride of place at that time as an emerging, competitive, and glamorous field.

However, instead of practicing as a veterinarian and making lots of money as such, my destiny was decided for me when, having topped my class, I was given the honour of joining academia – a prestigious field reserved only for those selected to be the best future teachers and researchers. I have had no regrets and have enjoyed every minute of my career.

## A PASSION FOR MAMMALIAN REPRODUCTIVE BIOLOGY

It was in the final year of my Doctor of Veterinary Medicine program that I developed a passion for mammalian reproductive biology (both human and animals). Having acquired expertise in animal reproductive biotechnology, I wanted to pursue a postgraduate program in human reproductive biotechnology

to make myself an all-rounder. My achievements of a couple of distinctions in my undergraduate subjects together with being top of the class earned me a Commonwealth Scholarship to pursue my postgraduate studies in Canada. I obtained an M.Sc. degree by course work and research in 1973, followed by a Ph.D. in 1976 from the prestigious department of biomedical sciences at the University of Guelph, Ontario, Canada. I was awarded the Rogar-Stephenson-Boyce award for outstanding research at the University of Guelph in 1974 and was among the very few students awarded a distinction merit rating for their Ph.D. degrees, having obtained straight A's in all my 15 course modules and a unanimous verdict from the five examiners who examined me during the defense of my thesis.

I learned the ropes of doing good research and the skills of scientific writing from an eminent supervisor, Emeritus Professor Pari Basrur, who was at the time one of North America's leading scientists. Under her guidance, I was fully equipped with the skills and knowledge involved with the handling and manipulation of sperm, eggs, embryos, and cells and was eager to set forth on a research career in the field of human reproductive biology. My broad knowledge of comparative reproduction (animal and human) was to me an asset and a strong foundation upon which I could embark on a research career involving human life. It was the joy and excitement in finding something new that could be applied and benefit mankind in the shortest possible time that spurred me into biomedical research.

## BUILDING UP A NICHE AREA IN SINGAPORE

With this strong foundation of good undergraduate and postgraduate training, I brought all the expertise with me to Singapore in 1986, embarking thus on the most productive part of my career. After barely a year in the country, I took up Singaporean citizenship, for a whole host of reasons. First, I am an Asian at heart, and Singapore provided me with an environment that was very conducive to my way of thinking with respect to discipline, transparency, and meritocracy. Second, English (which is the only language in which I am fluent, having being born to a Dutch mother and a Sri Lankan father) as a spoken and official language helped me in a big way. In addition, there were the benefits that I continue to enjoy today – good infrastructure, facilities, efficient systems, ample research funding, and political and economic stability provided by a good government – besides a safe environment to bring up a family and a peaceful multicultural environment that makes you feel at home. What better heaven to pursue one's dreams?



### About the author:

Prof Ariff Bongso is Research Professor and Scientific Director of the Assisted Reproductive Technology Program at the National University Hospital.

I am indebted to the late Emeritus Professor Shan Ratnam who headhunted, found me, saw the talents in me, and brought me to Singapore to join his prestigious department of obstetrics and gynaecology at the National University of Singapore, in which I have spent my last 16 years. I joined a team of eminent infertility specialists who badly lacked a clinical research scientist to drive forward the scientific and research aspects of their program. The timing was right as I knew that I was not going to be a square peg in a round hole. Given my training and background, this was the ideal niche for me as I had access to research material, research funding, and the facilities. All I had to do was to build up a research and service team, dream creatively, share my research ideas with my team and drive R&D forward in the field of in vitro fertilization, which was my passion.

### **THE MAKING OF SEVERAL ASIAN AND WORLD FIRSTS**

There was no looking back as I went on to lead a team to achieve several Asian and world firsts and make Singapore a Center of Medical Excellence in the field of assisted reproduction. I helped to develop a novel in vitro system called co-culture where embryos were grown on a bed of human fallopian tube cells up to 5 to 6 days simulating the in vivo physiology of a fertile woman. Once these 5- to 6-day-old embryos were transferred back to the wombs of subfertile women, the pregnancy rates doubled those that were obtained after the conventional transfer of 2-day-old embryos. The world's first co-culture baby was born in 1991.

Before that, I was part of the team that produced the world's first micromanipulation baby in 1989, where sperm were injected under the shell of eggs in a patient whose husband had a hopelessly poor sperm count and who had no other recourse of fathering his own child. In 1992, I led a team to produce the world's first babies after (day-5) blastocyst transfer, and in 1997 the world's first babies after zona-free blastocyst transfer where the entire shell of the embryo was enzymatically removed before transfer to assist implantation in older women. Co-culture evolved into 5-day-old blastocyst transfer, which finally evolved and culminated in the world's first report on the isolation of embryonic stem cells from human embryos in 1994. These were leftover frozen embryos of pregnant IVF patients that were donated to me. I reported my findings on the isolation of stem cells from human 5-day-old embryos in the British Journal Human Reproduction in 1994. Today, embryonic stem cells, dubbed as the "mother of all cells," is a buzzword.

### **THE FOUNDING OF ESI, EMBRYONIC STEM CELL INTERNATIONAL**

Following my preliminary research on the isolation of stem cells from human embryos, I was acutely aware that the

next big step was to direct these cells to form human tissues in a laboratory dish for later transplantation therapy into patients. This required very special expertise in the biology of stem cell differentiation. There were very few such scientists with this expertise worldwide. My own background in this new area was scant, as I was basically an IVF specialist. I also realized that a large sum of research money was needed to push this area of research forward.

I searched in vain for good scientists in this specialized area for almost a year within Singapore. Believing that the only way forward then was to get leverage by forming an international research alliance, I invited friends and colleagues from the Monash Institute of Reproduction and Development in Melbourne, Australia, who were excited about my dreams. We formed a group of five founder scientists from three countries (my colleague Dr. Fong Chui Yee and myself from the National University of Singapore, Professor Alan Trounson and Associate Professor Martin Pera from Monash University, and Dr. Ben Reubini from the Haddassah Medical Centre in Israel).

I approached the government of Singapore for research funding of this international team by making several research presentations to Senior Minister Lee Kuan Yew and other top officials in the Singapore government, including Mr. Philip Yeo, chair of the then Economic Development Board, and Dr. Lily Chan, life sciences investment director also with the Economic Development Board. They were very quick to see the importance of this research and handsomely funded all of us by initially spinning off a company, Embryonic Stem Cell International, registered in Singapore and managed in Melbourne. The major investors were the Economic Development Board of Singapore (a funder of Next Wave Singapore) and a private group of Australian businessmen, as well as all three institutions to which the five founder scientists belonged.

We handed over our intellectual property to our respective institutions, which in turn transferred it to ESI. We invited another leading stem cell scientist, Dr. Christine Mummery from Hubrect in the Netherlands, into our research alliance. So, in essence, the government of Singapore is backing the research of not only Singaporean scientists but also that of scientists in Australia, Israel, and the Netherlands. I am delighted to have played a major role in the initiation of this international consortium and extremely grateful to Chairman Mr. Philip Yeo, Dr. Lily Chan, and the private Australian business group for their insight in recognizing the potential of this research and for coming forward spontaneously to fund us. I believed that given a shortage of human resources in Singapore due to our small size, the only way forward was to work with reputed international scientists so as to reach the major objective – treatment modalities for all the major incurable diseases plaguing mankind all over the world – fast.

## **TAKING A CLINICAL RESEARCH TRACK TO INNOVATIONS**

Working in a clinical department was the ideal setting for my philosophy of applied research. Basic research takes too long a time for me to see the fruits of my labour. I like to see results soon and hence enjoy clinical research. I am convinced that not all academics can be good researchers. Besides being gifted with the art of creative thinking, one needs to read a lot and work at the bench to see one's own results of research.

Conceiving an idea to me is the most important and difficult aspect of research. There are many who can do the job once the idea is conceived. There are the satisfying and frustrating moments in research. I do not believe in giving up even if an experiment failed. We need to question "why?" and continue to modify and pursue the objectives behind the experiment. I do not believe in "stamp-collecting" research where a piece of research is conducted just to publish a manuscript and inflate a CV. I believe that the piece of research must be useful to mankind, preferably short term. I believe that good teachers are usually good researchers because they are able to translate their research findings into their teaching and dissemination of knowledge. Of course lucid and articulate public speaking with good fluency in the English language are complementary advantages.

## **THE PRESENT AND BEYOND**

Now is the right climate for research in the life sciences in Singapore. I wish it came a bit earlier when I was much

younger. Currently, while being active in stem cell and IVF research, I am also busy training and sharing my expertise with a younger group of Singaporean scientists. The aim is to build a strong research team that can pursue my ideas into the future. I have with me a very intelligent, hardworking, competent, and extremely committed team of seven research and service personnel of whom I am proud. It certainly is a joy interacting and working with them. They were very carefully selected and nurtured. We are busy with providing a laboratory service for childless couples enrolled in IVF, refining the in vitro systems for large-scale ES cell production, studying the genomics of these mysterious cells for direction into desirable tissues for clinical application later, finding other ways of improving pregnancy rates for older childless couples, and so on.

The Singapore government's drive in the life sciences has made research funding no problem at all. Ethical and commercial issues have been put well in place and I think there is no better place than Singapore right now for one to commercialize and pursue one's research dreams. I am fortunate to be part of Singapore's life science drive and I see in the future a tremendous success in Singapore's fourth economic pillar – the life sciences – simply because of the tremendous commitment and support from the government, together with the right and committed people at the top and a very dedicated group of local scientists who are competent to deliver. Singapore has all the money and infrastructure for research but what she lacks is the workforce in the form of good scientists. The few of us are stretched pretty thin, and until such time as our own scientists are trained we will have no choice but to import. ■