Improving IVF

In vitro fertilisation is the gold standard of infertility treatment and Dr Nathan Treff hopes to open new avenues by further advancing and enhancing the technique.

How did you come to develop your interest in molecular genetics and subsequently apply this to reproductive biology?

I obtained my PhD in Biochemistry from Washington State University (WSU) while researching the development of breast and ovarian cancer, and this is when I first became interested in molecular genetics. The technologies I incorporated into my research at WSU – DNA arrays and quantitative polymerase chain reaction (PCR) – were instrumental to my successes in postdoctoral fellowships, which focused on embryonic stem cell biology at the University of Wisconsin-Madison and reproductive biology at the Serono Research Institute.

Improving these technologies in order to enhance clinical care in reproductive medicine at Reproductive Medicine Associates of New Jersey (RMANJ) has been one of the most rewarding opportunities in my career.

In vitro fertilisation (IVF) success rates at RMANJ are significantly higher than the US national average. How does your laboratory contribute to this achievement?

Most IVF programmes outsource genetic testing, and for only a very small percentage of their patients. At RMANJ, my laboratory provides our patients with direct access to the most highly validated method of comprehensive chromosome screening (SelectCCS), which is utilised by over half of our patients.

How are you hoping to improve SelectCCS?

We continue to improve SelectCCS by incorporating innovative technologies such as next-generation sequencing (NGS). Sequencing the human genome 10 years ago cost billions of dollars and took many years to complete, but can now be done within a single day for circa $1,000 using NGS.

These cost-saving technologies are now possible in the field of IVF and genetic testing, and we are the first group working to accurately translate this technology into a clinical reality.

You currently hold the Associate Professorship at the Rutgers-Robert Wood Johnson Medical School. To what level have you included students in your work?

My laboratory helps train students at all levels of education, from the high school student interested in genetics, to the reproductive endocrinology and infertility fellow training to become a specialist physician in reproductive medicine.

At all levels, we are dedicated to teaching research integrity and the scientific process, and providing a real opportunity for discovery.

Current studies include the development of a more sensitive method for diagnosing spinal muscular atrophy (SMA) carrier status, determining the utility of SelectCCS in patients who produce very few eggs and identifying additional genetic biomarkers of reproductive health.

You were recently awarded the Ira and Ester Rosenwaks New Investigator Award by the American Society for Reproductive Medicine (ASRM). What was this in recognition of, and what does the accolade mean to you?

It is a great honour to have been recognised by ASRM for this award as it’s one of only three major awards given by the society each year.

There are so many people who helped me to reach this position and I think it also means a lot to the family, friends, colleagues and mentors who have supported my life and career. Now begins the hard work of living up to the award and continuing to accomplish new advances in reproductive medicine and genetics.

Are there any forthcoming events, conferences or workshops related to your research that you would like to highlight?

I will be giving invited lectures at the Second Biomarkers in Reproductive Medicine Meeting in Valencia, Spain, on 11 April 2014, and at the International Society for Preimplantation Genetic Diagnosis Meeting in Canterbury, England, on 2 May 2014. The focus of both talks will be the ongoing evidence that CCS is an effective strategy to improve the success of IVF.

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ON 25 JULY 1978, Louise Brown was born in Oldham General Hospital. While approximately 370,000 children are born worldwide every day, this five pound, 12 ounce baby was a very special case; she was the first human baby to be conceived using what is now known as in vitro fertilisation (IVF).

Over the decades that have followed, an estimated 5 million babies have been born using this breakthrough method, and significant steps have been taken to improve the success rate of IVF. Despite being the most effective treatment of infertility, which affects one-in-six couples, a 2009 report by the Centers for Disease Control and Prevention (CDC) in the US estimated that only 19 per cent of transferred embryos lead to healthy deliveries.

For this reason, a team at the Reproductive Medicine Associates of New Jersey (RMANJ) has been utilising new methods in an attempt to enhance the screening process for identifying healthy embryos and thus increase success rates. Pioneered by Drs Nathan Treff and Richard Scott, the team at RMANJ believes that quantitative polymerase chain reaction (qPCR) can now be used for fast and effective comprehensive chromosome screening (CCS) of potential IVF embryos.

IN VITRO FERTILISATION

As the name would suggest, IVF is the process whereby a sperm fertilises an egg in vitro, or outside of the body. The process involves monitoring and stimulating a woman’s ovulatory process, removing the resultant ovum or ova from the ovaries and allowing them to be fertilised by sperm in a fluid medium within a laboratory. This fertilised egg (zygote) is then cultured for two to six days in a growth medium, before being transferred to the patient’s uterus with the intention of establishing a successful pregnancy.

While this has become somewhat of a gold standard for assisted reproductive technology (ART), there are still flaws in the technique, which become especially pressing when one considers the huge financial, emotional and physical burdens for the couple attempting IVF. These issues can come, in part, from a lack of predictive testing. This can lead to unsuccessful implantation or delivery attempts. “The current standard at most IVF practices in the US is multiple embryo transfer without any genetic testing; these programmes are essentially rolling the dice,” Treff explains. “They have no idea whether none, one, two or more of the embryos transferred will implant or deliver.” For this reason, Treff and his team now hope that a new method of genetic screening can be utilised to identify potential embryo candidates, leading to a higher success rate in this commonly used method of reproduction.

While this kind of genetic screening is not completely novel to the field, the existing CCS
methods, which often combine various DNA quantification techniques, are often slow (≥12 hours) and ineffective. In an attempt to combat this, qPCR can be utilised in a method known as SelectCCS.

SelectCCS

While multiple markers are used in the screening of embryos in IVF, few have been wholly effective across the board. Nevertheless, one that has shown promising results thus far has been the identification of chromosomally abnormal (aneuploid) embryos.

Aneuploidy is the most common cause of implantation failure and miscarriage, and is known to increase with maternal age, mirroring the natural decline in fertility among human females. Moreover, the existing methods of embryo selection – which are often based on temporal and morphological microscopic appearance – are unfit for identifying embryos with abnormal numbers of chromosomes.

Thus, SelectCCS, which assesses all chromosomes in the embryo, offers advantages both in accuracy of determining the probable outcome but also, as explained by Treff: “Being able to perform this procedure in four hours significantly enhances the ability of the clinical team to perform embryo transfer during the most optimal time window of uterine receptivity”.

Before this method could be utilised in a clinical setting, Treff needed to first validate it as part of a multiphase testing strategy. Thus, in a 2012 paper that appeared in Fertility and Sterility, Treff and his team assessed the consistency of qPCR diagnosis of aneuploidy in nine cell lines with previously well-characterised aneuploidies. As hypothesised, this method produced promising results (97.6 per cent consistency) when compared with other existing methods. Furthermore, the goal of accurately screening for aneuploidy in all 24 chromosomes was achieved.

Having established an accurate technique, the next phase for Treff and his team came in determining both the negative and positive predictive values of SelectCCS for clinical outcome. From an experimental group of 146 couples, a total of 255 IVF-derived human embryos were cultured and selected for transfer without CCS analysis. Before this could happen though, the embryos were biopsied for DNA fingerprinting and aneuploidy assessment in order to assess whether SelectCCS would have been predictive of the actual clinical outcomes.

This study again produced promising results, as the researchers found that SelectCCS was highly predictive of clinical outcome, with 96 per cent of aneuploidy-predicted embryos failing to sustain implantation. Additionally, a further 41 per cent of embryos predicted to be chromosomally normal sustained implantation.

CLINICAL TRIALS

As with all treatment-centered research, the ultimate goal of these studies will come in deriving a clinically applicable technique. Thus, the next step for Treff and his team was to assess the clinical efficacy of SelectCCS in randomised controlled trials (RCTs). The first of these hoped to determine whether this method of SelectCCS could be used to improve IVF implantation and delivery rates. Using blastocyst biopsy, Treff found that sustained implantation rates were significantly higher in the CCS group (66.4 per cent) compared to those from a control group (47.9 per cent). Further to this, delivery rates were also greater in the CCS group, with 72 treatment cycles using CCS leading to delivery (84.7 per cent) compared to control (67.5 per cent).

While these results show great promise, Treff still wanted to assess whether this method was more effective than existing techniques, namely that of multiple embryo transfer, which can often increase the risk of multiple gestations. Thus, he opted to test the efficiency of the SelectCCS single embryo transfer compared to the transfer of two untested blastocysts. As predicted, Treff found that this method resulted in ongoing pregnancy rates that were the same as transferring two untested blastocysts but importantly, eliminated twin pregnancies.

These tools are now being applied to real-life clinical settings, no more so than at RMANJ. Widespread use of SelectCCS has resulted in dramatic improvements in overall success rates, reducing miscarriage rates, and reducing costs and complications normally associated with IVF pregnancies,” Treff elucidates.

Treff and his team believe that aneuploidy is only one potential biomarker candidate in improving screening and overall success of IVF. “We are now investigating whether other molecules, such as proteins and RNA, might be further predicative of a successful outcome amongst chromosomally normal embryos,” he concludes.

“This is a huge advantage that is paving the way for improvements in the success of IVF.”

INTELLIGENCE

REPRODUCTIVE MEDICINE

ASSOCIATES OF NEW JERSEY

OBJECTIVES

To develop state-of-the-art molecular biology based technologies that will improve the success of IVF and the treatment of infertility.

KEY COLLABORATORS

Dr Mandy Katz-Jaffe, Colorado Center for Reproductive Medicine, Lone Tree, Colorado, USA • Dr Antonio Capalbo, GENERA Reproductive Medicine, Rome, Italy

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