

Metris Therapeutics: a pharmaceutical focus on gynaecology

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Women account for more than half of the world population and can suffer from several female-specific conditions that, although not life-threatening, can result in a major decrease in quality of life and have a serious impact on socio-economic factors. Metris Therapeutics is developing novel therapies to assist in the management of these conditions; it represents a significant market opportunity as well as improving the quality of life of those affected.

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▼ Metris Therapeutics was originally established to develop a specific pharmaceutical approach for the treatment of endometriosis. It has significantly extended the indications for which it is developing novel pharmaceuticals, but has retained a close focus on its goal to develop innovative therapies to treat diseases and conditions that affect women. In particular, the company is developing products for benign gynaecological conditions. This article describes the aspirations of Metris and outlines its relatively unique approach to drug discovery and development. A small but vital team identifies and validates the novel therapies, and then project directors manage third-party resources to ensure a swift progression through the development process.

The beginning

When Metris was formed in 1996, it concentrated on the treatment of endometriosis, which significantly affects the quality of life of women. Although there are existing medical and surgical approaches for the treatment of the condition, they are far from ideal. The pharmaceuticals in use today work by suppressing oestrogenic activity. They can only be used for limited periods of

time because of side effects, such as reduced bone density. It is estimated that 4–17% of post-menarchal females have some degree of endometriosis [1] and this number would seem to be increasing as more accurate diagnostic procedures are made. In North America, it is estimated that 5.5 million women suffer with the condition [2]. Pain is the most common reason for presentation; infertility, dyspareunia and menstrual disorders are also frequently encountered. In the UK, endometriosis causes the loss of 45 days' work on average each year for every patient.

During the female ovulatory cycle, the endometrium becomes greatly thickened with increased numbers of cells and blood vessels; this is in anticipation of the implantation of a fertilized egg. If the latter does not occur then the thickened endometrial layer disintegrates and is shed in the menstrual flow. Endometriosis is thought to arise when cells from the endometrium are not voided but travel via the fallopian tube into the peritoneum. Following this process of 'reverse menstruation', the cells adhere to different healthy tissue surfaces and begin to proliferate and develop into significantly sized lesions. Although some of these are asymptomatic, many result in pain and the other symptoms described earlier.

The founding technology

Vascular endothelial growth factor (VEGF) is a potent factor involved in angiogenesis, stimulating the growth of endothelial cells by binding to receptors on the cell surface. The founders of Metris were the first to identify that VEGF is increased in the peritoneal fluid of women with endometriosis [3]. They postulated that endometriosis is dependent on angiogenesis and therefore the disease could be treated using

Box 1. Board of Directors and Scientific Advisory Board of Metris

Board of Directors

Michael Carter, Chairman
 Ann Hacker, Chief Executive Officer
 Kate Bingham, Non-executive Director
 Peter Knox, R&D Director
 Susan Lambert, Non-executive Director
 David Moorhouse, Chief Financial Officer
 Alain Munoz, Non-executive Director
 Stephen Smith, Non-executive Director
 Francis Upchurch, Medical Director

Scientific Advisory Board

Stephen Charnock-Jones^a
 Linda Giudice
 Bruce Lessey
 Kevin Osteen
 John Rock
 Stephen Smith^a

^aThese members are also founders of Metris.

molecules designed to prevent VEGF from binding to its natural receptors located on the surface of endothelial cells.

Metris has patented a series of molecules that have been shown to bind specifically to VEGF and is developing these anti-angiogenic molecules to provide a therapy for the treatment of endometriosis. The lead compound, which is in pre-clinical development, is a truncated form of the extracellular domain of a VEGF receptor. This agent has shown potent activity in several surrogate models (various models of endometriosis have been developed, but for practical reasons they have only limited use in pharmaceutical development).

The business strategy

Metris spent the first two years in research laboratories in Addenbrooke's Hospital (Cambridge, UK) with 'seed-corn funding' from Johnson & Johnson Development and Biotechnology Investment (Rothschild). Following a brief sojourn at a nearby laboratory in Cambridge and having secured its first major investment from the original investors and Schroder Ventures, the company moved to a facility equipped for its needs in the Winnersh Triangle Research Park near Reading (UK). In 2000, a second round of funding was obtained from Sofinnova, 3i Group and Northern Venture Partners, in addition to all of the original investors. To date, Metris has received £16 million in funding. The list of members

of the Board of Directors and Scientific Advisory Board of Metris can be found in Box 1.

For the past year and a half, Metris has been expanding its portfolio. It has established its own programmes but has also back-filled the pipeline with products that are closer to market; this has been achieved by in-licensing and by 'indication-switching' for pharmaceuticals already established in the marketplace. Currently, Metris has a treatment for menopausal symptoms soon to complete Phase III clinical trials, and novel approaches for the treatment of dysmenorrhea and endometriosis both entering the clinic within the next year. The next most likely candidate to enter full development will be for the management of abnormal uterine bleeding; this is an area that undoubtedly represents an unmet clinical need and is a major focus for Metris. Initially, the company will commercialize its products through organizations with a well-established franchise in women's healthcare.

This portfolio expansion has involved building up a small team with a skills base focussed on benign gynaecology. Whenever possible, development activities are performed under contract by other organizations. Functions such as toxicology, clinical trials and manufacturing are managed closely by a project director, who remains firmly within the Metris structure and liaises with the third party to ensure that the relevant workstreams are accomplished to a satisfactory quality, on time and also within budget. There is a clear distinction between activities that require specialist gynaecological experience and those that can be better accomplished by a skilled contract research organization.

Future strategy

For the foreseeable future, Metris will focus on clinical indications for which the pathophysiology arises in the female reproductive tract, in particular, the uterus. The company is therefore building and maintaining expertise in:

- the molecular and cell biology of the female reproductive tract;
- an understanding and use of model systems;
- rapid and efficient pre-clinical and clinical development; and
- project management.

It is important to stress that Metris has become expert in the identification and development of pharmaceuticals for its targeted indications. This is where the company adds value. The choice of whether to carry out a particular activity in-house or by contract is totally pragmatic. As a result of the above, the company now has one product in Phase III trials and two others will be entering Phase I in 2002.

Dysmenorrhea

One development programme underway is a novel approach for the treatment of dysmenorrhea, which is caused by powerful

uterine contractions and ischaemia of the myometrium and endometrium [4]; prostaglandins are responsible for most of these effects [5,6].

Metris is developing a new treatment for dysmenorrhea which is delivered locally via the vagina. This route of delivery benefits from the direct circulatory link to the uterine muscles; this also avoids hepatic clearance. It is therefore expected that side effects can be avoided using this route. The pharmaceutical has been widely used for the treatment of dysmenorrhea, but in a high-dosage oral formulation. The Metris approach makes use of a device containing a low dose that is delivered locally. The device also has the ability to absorb the blood and tissue that is lost at the time of menstruation. The device has shown an excellent profile in pre-clinical studies, and clinical trials for the device will begin in the USA in early 2002.

Menopause

Metris is also developing a convenient once-a-day oral treatment for the relief from symptoms associated with the menopause. The product is a proprietary combination of oestrogen and progestin; the choice of agents has enabled an expedited development programme. The product is aimed at patients with an intact uterus who require continuous chronic therapy. Metris has chosen a balanced combination of hormones that are expected to have an excellent efficacy and safety profile without the risk of endometrial hyperplasia. Patient recruitment is complete for a pivotal Phase III European trial, which will be complete in the middle of 2002.

Concluding remarks

Metris will continue to focus on a number of common gynaecological conditions that, although not life-threatening, can result in a distressing reduction of quality-of-life. There are also significant socio-economic consequences. These conditions can be difficult to study and this is one of the reasons for the limited attention they have received from the pharmaceutical sector. An increased understanding of the biology of the female reproductive tract is essential. This, combined with an infrastructure that ensures rapid progression through clinical trials and registration, leads Metris to believe it will be successful in its target areas of research and development.

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