Temple Therapeutics BV
www.templerx.com

Solving a sticky fibrotic problem

Temple Therapeutics BV's first-in-class phase-3-ready drug candidate for postoperative fibrosis is ready for partnering for an untapped $5 billion market.

In spite of numerous advances in the surgical sciences, postoperative fibrosis (POF), referred to in surgical practice as adhesions, continues to plague even the most experienced surgeons and greatly affects the outcomes of operations, as well as patients' quality of life. POF has been estimated to occur in up to 93–97% of surgeries, with one-third of cases leading to complications that require readmission and re-operation. Indeed, such surgical complications in the United States are estimated to cut hospital profit margins from 5.8% to just 0.1%, and hurt quality ratings and reimbursement rates.

Although the incidence of POF has been somewhat reduced by the use of minimally invasive surgery, it continues to be associated with significant morbidity and mortality. In fact, the global cost of adhesive pathology is estimated to be somewhere between $2.5 billion and $5 billion a year.

POF manifests as inappropriate growths of fibrous tissue that form after insults such as surgery, ischemia, infection or trauma. Such injury often leads to hypoxia, which robs tissues of oxygen and nutrients, and triggers an inflammatory cascade within six hours of the insult (e.g., abdominal surgery). Prolonged hypoxia and tissue damage from surgery play key roles in adhesion formation, at least in part by inducing the release of known fibrotic mediators such as HIF1a, TGF-β1, TGF-β2, VEGF, tPA and PAI.

To date, the only options available to curb POF formations have been synthetic polymers designed to prevent intra-abdominal surfaces from touching, thus removing the opportunity for fibrous tissue to form. However, these have drawbacks in terms of their ease of use, safety and efficacy.

It is this unmet medical need that is the focus of Temple Therapeutics BV, a private drug development company, based in Geleen, the Netherlands. The company is developing a novel therapeutic approach to prevent or significantly reduce POF, thereby reducing downstream complications for the patient such as pain, infertility and bowel obstruction.

Temple's novel approach is to address the balance in cytokine response to surgery by using a dipeptide, alanyl glutamine. The compound, which was originally identified for this purpose at a Canadian university, has been licensed exclusively by Temple.

Restoring cytokine balance

How does a single, acute treatment such as Temple's Evitar (L-Alanyl-L-Glutamine) which is applied at the time of surgery, prevent or ameliorate a process that takes weeks and persists for years? Evitar (which means "to prevent") is thought to work by redirecting metabolomic signalling to restore cytokine balance at the cellular level within a few hours of surgery. This immediate and crucial intervention blocks the trigger to the inflammatory cascade of cytokines and factors that promote fibrous formation, thereby preserving tissue homeostasis and, ultimately, promoting normal healing.

Evitar has completed a double-blind, placebo-controlled, randomized study with both a laparoscopic arm ($n = 38$) and laparotomy ($n = 10$), both randomized 1:1 in myomectomies (removal of fibroids) with 6–8-week post-op laparoscopy second-look follow-up, which is the gold standard for assessing fibrous tissue. Myomectomy is the surgical removal of fibroids from the uterus. It allows the uterus to be left in place and, for some women, makes pregnancy more likely than it would be without the surgery.

Gynecology-related POF is the leading cause of secondary infertility in women, with 15–20% of cases attributable to POF.

Because the approach is innovative, the US Food and Drug Administration (FDA) wants the company to focus on a narrower clinical endpoint than reduction of POF. So instead of a first-in-class drug to reduce POF after gynecological or abdominal surgery, as initially proposed, the company is potentially looking at a first-in-class drug that enhances fertility for patients undergoing myomectomy by reducing POF.

"Either way, it makes it very attractive to fertility specialists, surgeons and payers, and women who are looking to have a family," said COO Lynne Robertson. "Clinically relevant outcomes are also attractive to payers, providers, partners and financiers; it strengthened our patents as a bonus, as well."

Ready to codevelop

As it considers phase 3 development, the company is looking for a codevelopment partner, the selection of which will be governed by indication. "In myomectomies, we would be looking for a partner that understands the hospital space, women's health, fertility, has experience with the FDA/EMA in running phase 3 trials and an appropriate commercial infrastructure," said Robertson.

In return for rights to a particular territory, Temple anticipates that a partner would pay for the phase 3 development and manage regulatory submissions, while Temple would continue to manage the leading clinical key opinion leaders. "That is the ideal but there [are] a lot of different ways we could partner. We see codevelopment as probably the most efficient way to proceed," Robertson added.

Beyond the readout of the current trial, the company expects to achieve the following this year: file the investigational new drug (IND) application; raise up to $25 million, preferably from non-dilutive sources; complete applications for orphan drug designations; and publish three papers in the gynecology area in peer-reviewed journals. The company is moving ahead with two animal studies and the publication of papers covering POF prevention in spinal indications, and it is gearing up for a human study in 2018.

"POF has historically been the nemesis of surgeons for centuries, a nightmare for patients, and a burden to providers/payers. No one has really found a safe, effective solution and no one has used a drug. Using a drug to address the underlying biology is novel and we are excited about its potential applications and impact," concluded Robertson.

contact
Lynne Robertson, COO
Temple Therapeutics BV
Geleen, the Netherlands
Tel: +1-401-744-2718
Email: lynne@templerx.com