AnGes MG

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Innovative therapy for critical limb ischemia

AnGes MG is poised to create a new drug market with Collategene.

Critical limb ischemia (CLI), the severest form of peripheral arterial disease (PAD), is a growing global health issue for which amputation of a lower limb becomes unavoidable in the worst cases. Collategene, a plasmid DNA encoding hepatocyte growth factor (HGF) developed by AnGes MG in Japan, is now poised to fill a void for patients who are poor candidates for existing treatments such as endovascular interventions or vascular bypass surgery.

AnGes, founded in December 1999 as a spin-out from Osaka University, is a clinical-stage biopharma company that focuses on the development and commercialization of novel gene-based medical treatments including gene therapy, DNA vaccines, oligonucleotides and proteins for diseases with high unmet medical needs. Collategene is a gene therapy.

HGF promotes angiogenesis in the body. When Collategene is injected directly into the skeletal muscle of the affected lower limb, HGF protein is expressed within the transfected cells and secreted, prompting angiogenesis (**Fig. 1a**). The formation of new blood vessels improves blood flow to the limb (**Fig. 1b**).

AnGes has targeted CLI (a condition caused by severely reduced blood flow to the legs, which results in severe pain, ulcers or necrosis) because the medical need is both urgent and largely unmet. Currently, there is no effective drug for late-stage patients, who face costly amputation, a highly compromised quality of life and an abnormally high mortality rate.

Revascularization, by methods such as surgical bypass and angioplasty, is the current first-line therapy for more than 85% of newly diagnosed CLI patients. However, despite the prevalence of the treatment strategy, revascularization is not advisable in approximately 40% of chronic CLI patients because of the location of lesions, the extent of the disease, extensive comorbidity or previous failed attempts at revascularization. Patients who are not eligible for revascularization will most likely undergo amputation or die within 2 years. The 3-year post-amputation survival rate in CLI patients is less than 50%, and up to 20% of amputees ultimately require permanent nursing home placement.

Global phase 3 clinical trials to investigate Collategene for the treatment of CLI have commenced in the US and the EU. In addition to offering significant patient benefits, the drug could have a major impact on global health economics by reducing the health care costs associated with CLI.

"There are an estimated 500,000 new patients with CLI annually in the US alone, and this figure is growing," said Ei Yamada, president and CEO of AnGes. "If they are unsuited to existing surgical interventions, the cost of an amputation is more than $50,000, with ongoing annual medical costs of $40,000 per amputee. This could be reduced by more than 50% with limb salvage by Collategene."

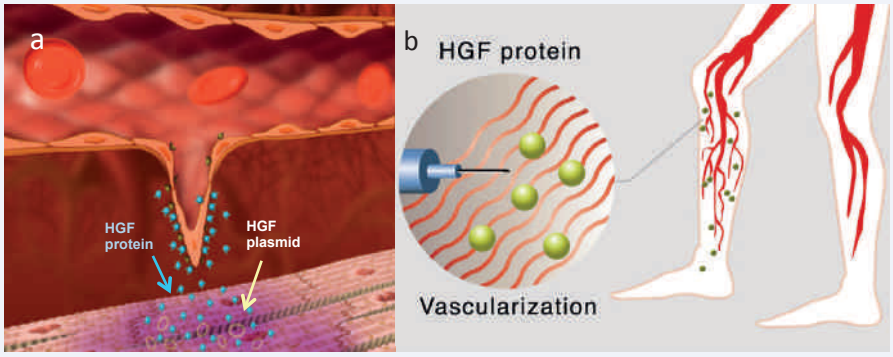

Figure 1: Gene therapy for CLI. (**a**) When Collategene, a plasmid DNA encoding HGF, is injected directly into the skeletal muscle of the affected limb, HGF protein is expressed within the transfected cells and secreted, prompting angiogenesis. (**b**) Vascularization improves blood flow to the affected limb.

The increase in CLI cases is believed to be between 2.5% and 3% annually in the developed world. Several societal drivers are fuelling this increase, including aging populations and growing incidences of diabetes, obesity, smoking, hyperlipidemia and hypertension. The disorder is also a serious problem in some developing countries where diabetes is becoming more widespread and smoking is still popular. CLI often goes undiagnosed in both the developed and the developing world, particularly among the poor. The disease is most common in men aged more than 60 years.

The lifetime risk of a person with diabetes developing a foot ulcer could be as high as 25%, and it is believed that every 30 seconds a lower limb is lost somewhere in the world as a consequence of diabetes[1].

PAD is also strongly linked to aging, with one study estimating that the prevalence of PAD in the US is approximately 1.3% in men and 1.7% in women aged 40–49 years but then leaps to as much as 29.4% in men and 24.7% in women aged more than 80 years[2].

CLI has proved challenging to biopharma companies because of past development failures linked to vascular endothelial growth factors and fibroblast growth factors, which have been the most widely studied factors for neovascularization.

"Collategene has been our core project since the company's establishment," Yamada elaborated. "As a potential first-in-class and best-in-class treatment, Collategene will herald a new drug market, the potential of which is estimated at $5 billion. The realization of Collategene is an important step toward our company's vision of becoming a global leader in gene therapy."

> **"Collategene will herald a new drug market."**
>
> **EI YAMADA**

Collategene is effective and safe in clinical trials

The efficacy and safety of Collategene have already been demonstrated in multiple clinical trials in Japan and the US. A global phase 3 clinical trial began in the US in October 2014, with the first patient dosed in November. Over 3 years, the trial will enroll approximately 500 subjects with CLI to be treated at a number of centers located in North America, Europe and South America. The US Food and Drug Administration has granted Special Protocol Assessment and Fast Track status to the trial because of Collategene's potential in treating a serious disease with unmet needs.

The therapy is the front-runner among potential CLI treatments, its cost is a fraction of that associated with stem cell therapy, and it does not require sophisticated facilities that would limit use to the developed world. Data from the global phase 3 study launched in November 2014 will be collected for application to US and European authorities, with the Biologics License Application targeted for as early as 2018 in the US, to be followed by applications in Europe.

The phase 3 clinical trial that took place in Japan demonstrated significant improvements in ulcer size for the treatment group compared to the placebo group (**Fig. 2**). Participants in the

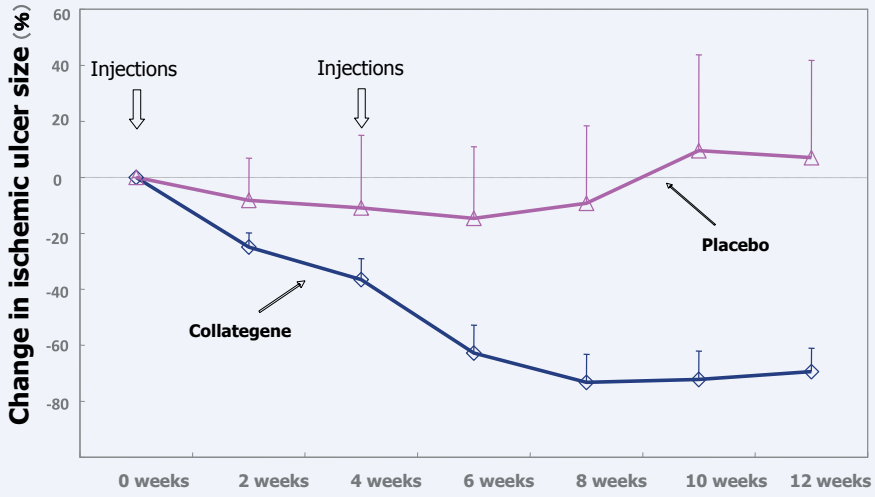

Figure 2: Observed clinical benefit. Collategene was investigated in a Japanese phase 3, double-blind, placebo-controlled study for the treatment of CLI. The graph shows the percent change (mean + s.e.m.) in ischemic ulcer size relative to baseline in patients with Rutherford stage 5 ischemia, a classification associated with advanced disease. A statistically significant reduction in ulcer size was observed.

Project	Pre-clinical	Phase 1	Phase 2	Phase 3	Market
HGF		Lymphedema Phase 1/2 (Japan)		Critical limb ischemia Global phase 3	
NF-κB Decoy oligonucleotide	Low back pain due to disc degeneration			Atopic dermatitis Phase 3 (Japan)	
In-licensed	Cervical dysplasia CIN therapeutic vaccine				MPS VI Naglazyme (Japan)
Medical devices			Vascular restenosis NF-κB Decoy Drug coated balloon catheter (Japan)		

Table 1: Product pipeline. The AnGes pipeline includes gene therapy, therapeutic vaccine and decoy oligonucleotide development candidates and the marketed therapy Naglazyme for the treatment of Mucopolysaccharidosis type VI (MPS VI). Gene therapy to promote hepatocyte growth factor (HGF) secretion and nuclear factor kappa B (NF-κB) decoy oligonucleotide have potential for the treatment of multiple indications.

study were suffering from CLI following occluded arterial disease and had exhausted all of the available treatment options. During the trial, Collategene or a placebo was injected directly into the affected limb twice at 4-week intervals. The study also demonstrated the safety of the gene therapy, as no serious adverse reactions were observed even after a follow-up period of 15 months.

"We believe Collategene could dominate the CLI market," Yamada said. "It is the most advanced product under development, and its effectiveness has been consistently proven in multiple trials. Quality of life for CLI patients would be improved dramatically by limb salvage, and the impact on global health economics would be very significant."

Partnerships sought

AnGes has its headquarters and laboratory in Osaka and offices in Tokyo, the US and the UK. AnGes has a combination of out-license and in-license agreements (**Table 1**). It has partnered with Mitsubishi Tanabe Pharma in the US for the commercialization of Collategene for CLI. Partnerships in the EU and the rest of the world are being sought.

Collategene also has potential in the treatment of other conditions such as ischemic heart disease (IHD) and lymphedema. AnGes has phase 1/2 lymphedema trials underway in Japan and has completed a phase 1 IHD trial in the US. Partnerships are sought globally to advance development for these additional indications.

AnGes has been marketing Naglazyme (galsulfase) in Japan since 2008. Naglazyme, which was in-licensed by AnGes from BioMarin Pharmaceutical, is a treatment for the rare genetic disorder mucopolysaccharidosis type VI (also known as Maroteaux-Lamy syndrome). The syndrome is a progressive condition caused by a complete or partial lack of activity of the enzyme arylsulfatase B.

An out-licensing agreement was struck with the pharmaceutical company Shionogi for nuclear factor kappa B (NF-κB) decoy. NF-κB is a transcription factor that regulates the immune response in inflammation and has a critical role in many inflammatory and immune diseases. Decoy oligonucleotides such as NF-κB decoy competitively inhibit binding of the target transcription factor to corresponding sites in DNA, preventing the expression of relevant genes. NF-κB decoy is an ideal pharmacological tool for selectively blocking NF-κB activation. AnGes is developing the therapy for the treatment of atopic dermatitis, for which a Japanese phase 3 trial commenced in March 2015.

Earlier stage programs include preclinical-stage work on the use of NF-κB decoy for low back pain due to intervertebral disc degeneration, as well as physician-led clinical research in Japan on a therapeutic vaccine against human papillomavirus for use in treating cervical intraepithelial neoplasia. Research is also being carried out on an angiotensin II DNA vaccine for hypertension and heart failure.

References

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