

Break on Through



Genetic medicine venture AnGes MG has a raft of innovative treatments and vaccines at the clinical trial stage.

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Ei Yamada's view of the pharmaceutical business underwent a sudden and dramatic change in the 1980s. Dispatched from Tokyo to San Francisco to represent a large Japanese chemicals-to-pharmaceuticals firm, one of his tasks was to set up a joint drug development project with Genentech, the U.S. biotech superstar. "Genentech could do things that took us a full year in just three months," says Yamada. "They moved fast and brought in leading outside experts from academia when necessary. That's the can-do mindset you need if you want to succeed in the

pharma business today."

This insight inspired Yamada to quit his stodgy, big-company job and make a sideways move into the dynamic world of ventures upon his return to Japan. After five years in a biotech startup, Yamada helped set up the Dragon Genomics Center, one of Asia's biggest genome analysis centers, then joined AnGes MG in May 2001 at the invitation of the founder, Professor Ryuichi Morishita. He was appointed president and CEO in 2002.

A specialist in cardiovascular medicine, Dr. Morishita had

set up AnGes in 1999 to commercialize his research at Osaka University. He launched the company with three distinct research themes: a genetic therapy for critical limb ischemia trademarked as Collatogene; a treatment for inflammatory diseases based on the NF- κ B decoy oligo; and finally, the hemagglutinating virus of Japan Envelope vector (HVJ-E) with its potential for drug delivery or cancer immunity.

"Setting up a new company with a single research theme would obviously

mean an excessive concentration of risk," Yamada explains. "Morishita deliberately chose three themes as a risk hedge."

The potential market is estimated at \$5 billion per year

Targeting ischemic disease with Collatogene

The HVJ-E business was later sold off, but AnGes' two other original research themes are still going strong. Indeed, the first of these—Collatogene, a genetic therapy for critical limb ischemia—is about to start Phase III clinical trials in the United States.

Critical limb ischemia, or CLI, is a complication that appears in the later stages of diabetes and other diseases. With the blood vessels of the lower limbs narrowing and blocking circulation, patients often have to have a leg amputated. (Worse still, some 40% of patients die within two years of amputation.) Collatogene's



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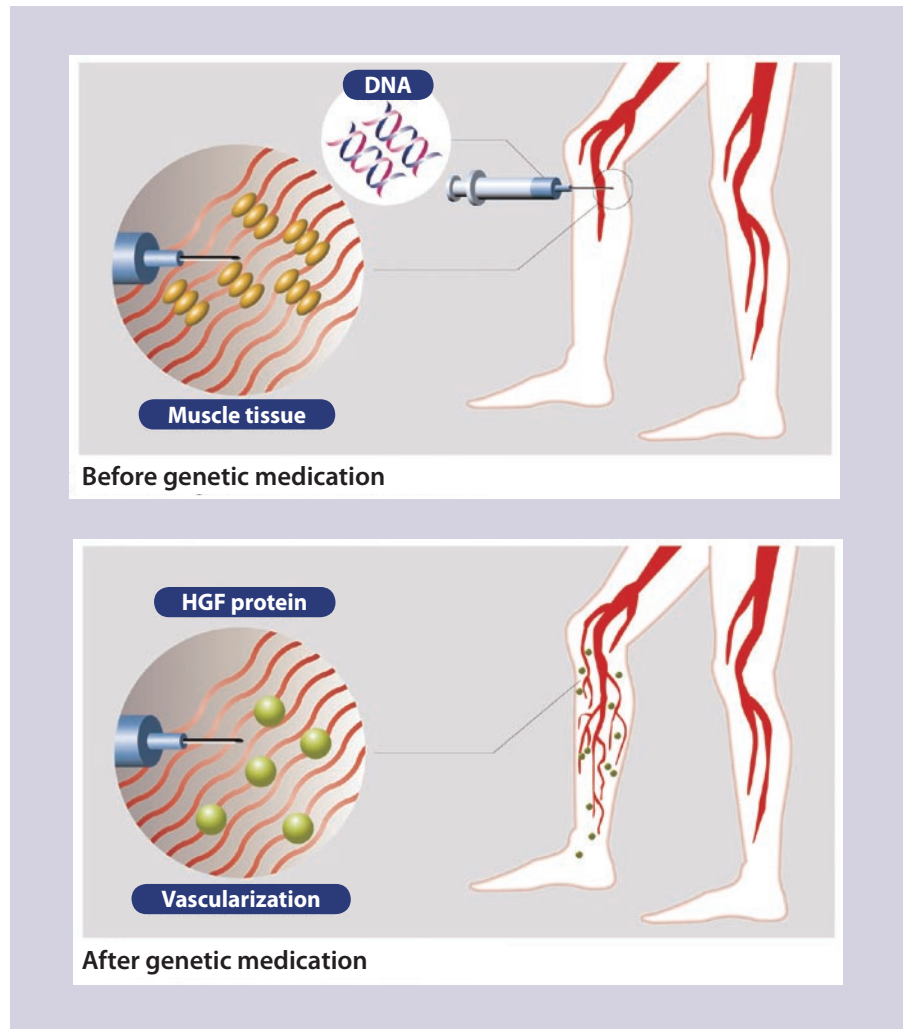
extraordinary vascularization abilities can revive the blood vessels and help avoid, or at least delay, amputation.

Being largely diet-related, diabetes is more common in the United States than in healthy-eating Japan. In Japan roughly 5,000 to 20,000 people have a leg amputated due to critical limb ischemia every year; in the United States, the equivalent figure is 300,000 people.

Sheer market size is one of the main reasons that AnGes decided to scrap the Japanese application for Phase III approval of Collatagene and go instead for certification in the United States. The different criteria by which the FDA in the U.S. and the Ministry of Health, Labour and Welfare in Japan judged the drug were another decisive factor. In Japan the endpoints of the trials were the degree of pain relief and the ability to get rid of ulcers. By contrast, in the U.S. the endpoint was how far you could extend the time up to amputation or death.

“From a marketing perspective, it makes more sense to target the US and get approval based on the American endpoints,” Yamada explains. “It will be advantageous internationally. U.S. approval means easier entry to Europe. Meanwhile, recent regulatory changes in Japan also inspired us to resume the development of Collatagene here as well.”

To raise funds to finance the clinical trials of Collatagene, AnGes secured ¥1.98 billion through issuing stock acquisition rights to Merrill Lynch. From October 18, it also issued further



rights to the London Branch of UBS AG. The potential overall market is estimated to be worth around \$5 billion per annum. “We want to be the first company to bring a treatment to market so we’re pushing forward with Phase III trials as fast as we can,” declares Yamada.

AnGes has already formed exclusive sales partnerships for Collatagene with Daiichi Sankyo for Japan and Mitsubishi Tanabe for the U.S., and is looking for a partner for Europe. Mitsubishi Tanabe and the prospective EU partner will help

fund the \$80 million development costs, paying cash upfront for development milestones now and percentage-based royalties later.

The multiple applications of NF- κ B

After Collatagene, the second of Morishita’s original research themes was NF- κ B, a kind of protein that clusters around specific genes causing “inflammation events.” (Diseases that occur when NF- κ B becomes dominant include atopic dermatitis,

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asthma, lumbago and arteriosclerosis.) Preventing NF- κ B from clustering can prevent inflammation.

AnGes's NF- κ B decoy oligo, a new formulation to treat atopic dermatitis, is currently undergoing Phase I clinical trials in Japan. AnGes has made a joint clinical development contract with Shionogi Inc.

A second NF- κ B product in clinical trials is an NF- κ B decoy oligo-coated PTA balloon catheter. This product is designed to treat vascular restenosis (a condition when the blood vessels narrow, blocking the flow of blood). A normal catheter forces open the blood vessel by inflating the balloon, but has the drawback that after the balloon deflates, the blood vessel reverts to its

previous constricted state.

By contrast, a balloon whose surface has been covered with a coating of AnGes' NF- κ B decoy oligo "converts a stopgap solution into a permanent solution," in Yamada's words. How so? When the NF- κ B decoy oligo coating is transferred from the inflated balloon to the inner walls of the expanded blood vessel, it stays there, hardens and keeps the blood vessel distended even after the balloon deflates.

Yamada is proud of AnGes' novel idea of putting a device and a drug together for combination therapy. AnGes' partner for developing this

The potential market for our CIN vaccine looks promisingly large

product is Japanese medical device company MEDIKIT. Clinical trials got underway in 2012.

Advancing through alliances

Whether MEDIKIT, Shionogi, Mitsubishi Tanabe or Daiichi Sankyo, finding the right partners with whom to develop treatments is a crucial element of Yamada's strategy. While the U.S. has a whole ecosystem in place to provide funds to startup companies, there is no similar "venture culture" in Japan yet. That means AnGes' partner companies play an essential role in shepherding its treatments through the extremely expensive and time-consuming process of clinical trials.

On occasion AnGes also brings in key technology from other biotech ventures. A case in point is the company's cervical intraepithelial neoplasia (CIN) therapeutic vaccine, (a vaccine for precancerous treatment of the cervix), for which the technology came from Korea's BioLeaders Corporation. AnGes has teamed up with the Obstetrics and Gynecology Department of the prestigious University of Tokyo Hospital to develop this.

How does the CIN vaccine work? "Human papilloma virus—or HPV—is what causes cervical cancer," explains Yamada. "The progress of HPV results in increased expression of the E7 antigen which turns normal cells into cancerous cells. Our CIN therapeutic vaccine suppresses this E7 antigen, thus suppressing the cancer."

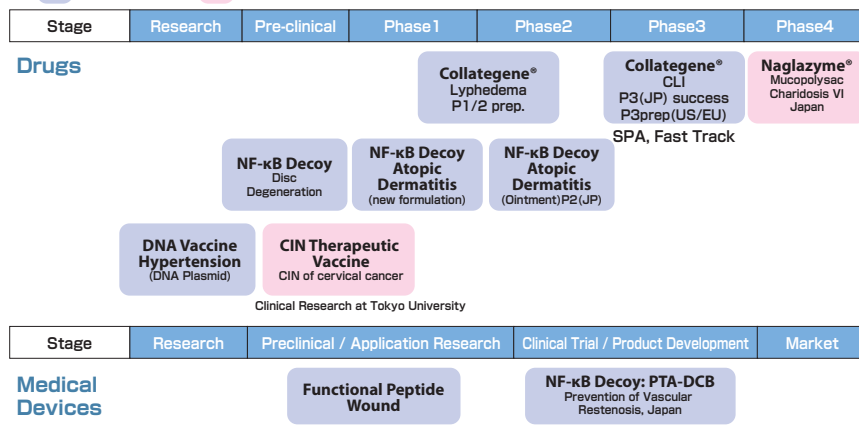


The University of Tokyo Hospital

AnGes MG Product Pipeline

- Multiple projects in pipeline: Diversification of risk
- Collatogene[®], a major CLI product, is entering the final stage

■ AnGes-origin ■ In-licensed



Again the potential market looks promisingly large. Three hundred million women worldwide are HPV carriers. This progresses to cervical intraepithelial neoplasia in 40 million cases, finally turning to cancer in 450,000 cases. Those 40 million women constitute the target market.

Other larger pharmaceutical companies have tried to make a CIN therapeutic vaccine—and failed. What is AnGes' secret? The company's breakthrough was to combine the E7 antigen with a lactobacillus (a bacteria which exists in large quantities in our gut anyway), enabling the vaccine to be taken orally. "Taking the CIN vaccine orally means it goes directly into the intestine," explains Yamada. "Since the intestine and the cervix are literally side-by-side in the body, the immune reaction provoked in the intestine travels through to the cervix, where it kills the E7-expressing cells that cause

cancer. No one could get this result with vaccines applied subcutaneously, because the E7 induced T-cells died before they could travel all the way down to the cervix."

HPV vaccines for warding off cervical cancer currently on sale globally have been found to have severe side effects, so there is a clear demand for an effective, but safe product.

Headwinds and tailwinds

Despite the positive outlook for AnGes' product pipeline, the company suffered a setback this August when Allovectin, an immune-induction cancer treatment vaccine for malignant melanoma, failed to secure Phase III clinical approval in the United States.

"It was a serious shock," admits Yamada. "We were expecting Allovectin sales to put the company into profit for the first time around 2015. I am no

longer confident that we will achieve that target."

Yamada now defines his task as "putting things right." He plans to launch Collatogene as fast as possible (though he concedes it won't generate the bumper profits Allovectin was expected to deliver), and is on the lookout for other products the company can put out quickly.

At present, AnGes has just a single product on the Japanese market. Named Naglazyme, it is a drug developed by

BioMarin of the U.S. to treat mucopolysaccharidosis VI (MPS VI). MPS VI is a rare disease that causes dwarfism, thickened skin, progressive joint stiffness and respiratory infections.

Although the nationwide market for Naglazyme consists of only five patients, Yamada insists that marketing the drug in Japan has been very worthwhile. "Thanks to Naglazyme, we've deepened our relationship with the Health Ministry, gained direct access to patients, learned about patient care and contributed to patient well-being."

A shot in the arm from Abenomics

The arrival on the scene of new Prime Minister Shinzo Abe with his stagnation-busting growth strategy is looking like a positive for AnGes. Abe is the first prime minister to incorporate the health care industry into his plans for growth.

Japan now accounts for less

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than 10% of the global market for pharmaceuticals. That’s because new drugs are what generate big sales—and Japan is failing to produce any. Abe wants to kick start pharmaceutical innovation in Japan by focusing on regenerative medicine (which includes AnGes’ area of gene therapy). Japan is a pioneer in the field with brilliant researchers like the Nobel Prize-winning Dr. Shinya

Abe's growth strategy is good news for AnGes

Yamanaka and innovative companies like Japan Tissue Engineering Ltd.

Abe plans to present a bill to the Diet this October to allow fast-track approval for new regenerative medicines. The new law will make it possible to launch products based on provisional data and secure formal and final approval based on the additional data gathered while they are on the market. “This is clearly good news for venture

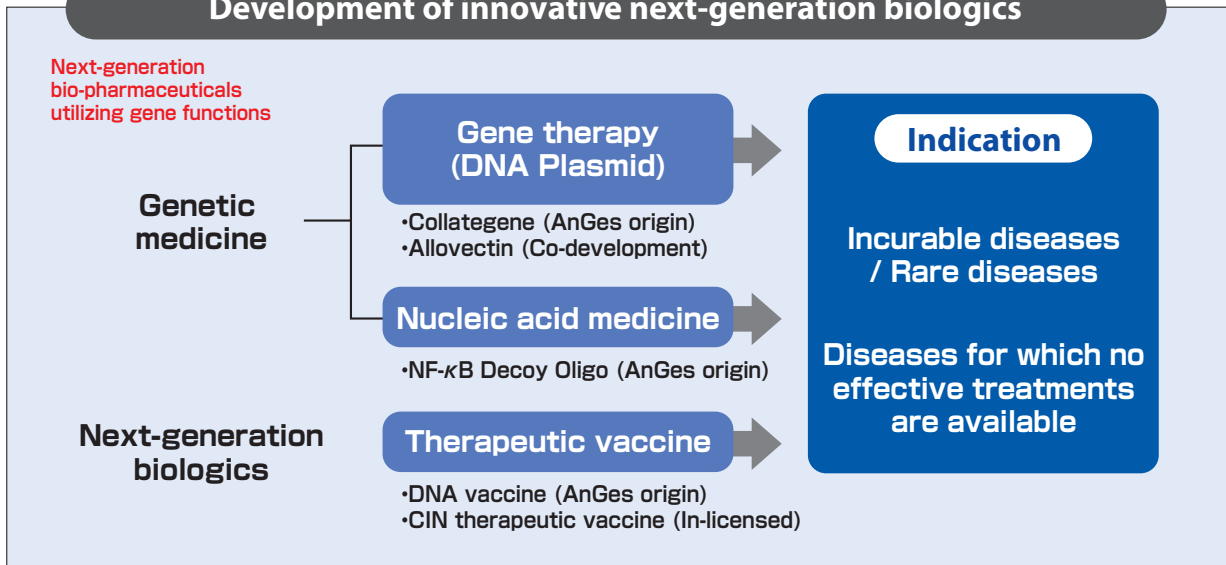
companies like AnGes,” says Yamada. “We expect to benefit from this change. It was certainly the decisive factor in our resuming the development of Collatogene in the Japanese market.”

With central government policy providing a tailwind, a promising pipeline of innovative products, and a brace of world-class partners, the next few years should see AnGes MG bringing products to market and getting a payoff for all the long years of research and development. ■

Corporate/Product Strategy: AnGes MG

- Novel drug development of biologics using advanced technology
- Innovative drug development for incurable diseases

Development of innovative next-generation biologics



Our company has a high proportion of individual investors. We've always done our best to communicate with them. We don't just hold seminars for our existing shareholders, we also take part in plenty of third-party seminars targeted at individual investors.

In fact, we take every opportunity we can to publish information about the company and communicate with our investor base. We upload anything that we're legally bound to disclose both to our own website and to bilingual investor-relations portal site IR STREET. As well as IR news, stock-price information from Yahoo! Finance, quarterly reports, securities reports, business reports and documents put out for the annual shareholders meeting, on our homepage you'll also find IP reports, recorded seminars available for streaming, an IR calendar for future events, media clippings and analysts reports.

This year we have been focusing on institutional investors and have done plenty of one-on-one meetings with them. Having raised capital from several institutions this spring, we need to prioritize communication with this group. At the end of September 2013, the proportion of stock held by institutional investors had risen, while the proportion in the hands of individual investors was down by 6.7%, compared to last year.

Going forward, we intend to use the bilingual IR STREET site to keep in close touch with our investor base. In particular, we mean to work hard to get all relevant news and data out in English in as timely as fashion as possible so we can deepen our communication with foreign institutional investors.



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Group Leader
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Established: December 17, 1999

Listed on: Mothers markets of Tokyo Stock
Exchange

Listing: September 2002

Fiscal Year-End: December

IR website: <http://www.anges-mg.com/en/index.html>

Capitalization: 11,552 million yen (at the end of
September 2013)

Issued and outstanding: 312,676 shares (at the end
of September 2013)
