35 YEARS

KYOWA KIRIN

La Jolla Institute FOR IMMUNOLOGY

Where Science Meets Solutions

# The Power of Partnership:

## A Story of Potential, Perseverance, and Profound Impact

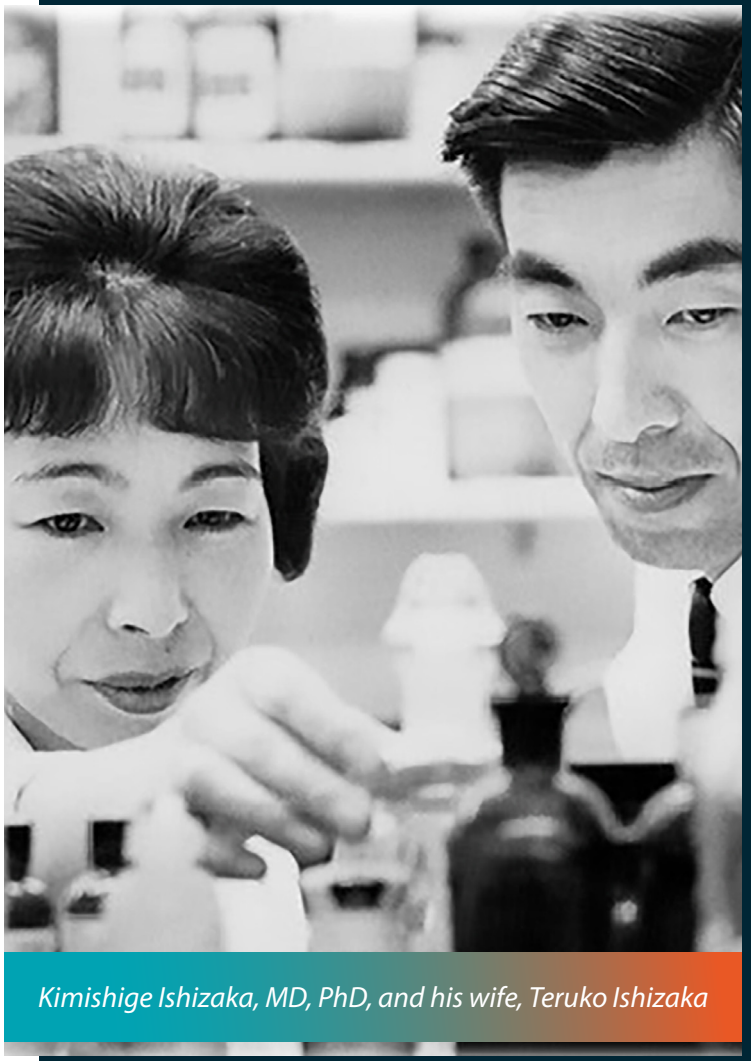
# An Idea **Takes Hold**

Biomedical research is an incremental endeavor. The cures we hail and the drugs we laud are born of painstaking trial and error, crushing defeats, then a monumental leap forward that brings clarity and focus to a vexing problem that once evaded the best and brightest minds.

By working together in an atmosphere of unbounded exploration, scientists can accelerate these discoveries and collectively advance knowledge to relieve human pain and suffering.

This collaborative spirit—the essence of 和 (Wa)—led a Japanese immunologist to propose a novel idea to Kyowa Kirin leaders in 1988.

"It all began when Dr. Makoto Nonaka decided to establish a nonprofit allergy and immunology institute, and he visited Kirin Brewery to look for a sponsor," said Toshifumi Mikayama, PhD, former Chief International Business Officer and Representative Director at Kyowa Kirin. "At that time, Kirin Brewery had already started a pharmaceutical business, but there were no products to sell, and their focus was on research and development. Kirin's top management decided to sponsor such a research institute to advance its scientific exploration and activities."



*Kimishige Ishizaka, MD, PhD, and his wife, Teruko Ishizaka*

**"Building an environment where world-class researchers can meet weekly and discuss appropriateness of drug targets based on cutting-edge scientific information is a wonderful thing."**

*- Toshifumi Mikayama, Ph.D*

# The Early **Days**

Kyowa Kirin's initial $3 million funding positioned Nonaka-san and his colleague—Kimishige Ishizaka, MD, PhD—to establish one of the world's finest research institutes, with a mutual understanding that its activities would be independent of Kyowa Kirin's.

Along the way, the organizations' research interests aligned, and the institute' s reputation steadily climbed, attracting top talent, including Douglas R. Green, PhD, Eli Sercarz, PhD, and Carl Ware, PhD. In 1997, Mitch Kronenberg, PhD, joined the institute, leaving a tenured faculty position at UCLA to seek an intriguing new challenge.

"I had a research lab, I had graduate students, and we were well supported," said Kronenberg, President Emeritus of the La Jolla Institute for Immunology (LJI). "The dean of the medical school, a very eminent physician scientist at UCLA, said to me, 'Mitch, why are you going to work for a beer company?' And I said, 'Dr. Shine, it's not a beer company, it's a research institute.'"

Perhaps because of their unique origins and Japan's cultural affinity for longevity, Kyowa Kirin and LJI took the long view; embracing the promise of future potential rather than fearing the peril of short-term risk.

"We didn't have any kind of financial security, no endowment—only the support from Kyowa Kirin, which supported the whole enterprise, the whole institute," said Kronenberg. "Each professor received—and still receives—funds to support their respective labs while writing grants to get big money."

# The Freedom to **Explore**

The unrestricted funds allowed LJI researchers to freely explore avenues of inquiry that might lead to remarkable discoveries or, alternatively, dead ends, with the hope that new learnings would lead to novel therapies or potential cures.

"Kyowa Kirin's annual funding allowed us to do amazing things, like work on a vaccine for heart disease, or one that prevents dengue and viruses in that family; ways to prevent T cell exhaustion in cancer, or how T cells lose their ability to respond to chronic inflammatory conditions," said Kronenberg. "The funding allowed us to go on tangents, but also to think in a more entrepreneurial way."

The open exchange of information enriches both teams through different types of thinking—fundamental research at LJI funnels into applied research at Kyowa Kirin.

"Our greatest value to Kyowa Kirin is our ability to bring about that novel mechanistic understanding of what has gone right or wrong in that cell; what is the right molecular target for drug development; and what is the difference between health and illness," said Erica Ollmann Saphire, PhD, MBA, President and CEO of LJI.

**"LJI enriches Kyowa Kirin through its depth of scientific exploration and technologic capabilities, while Kyowa Kirin enriches LJI through its focus on clinical applications, and its ability to transfer scientific discoveries into novel therapeutic interventions."**

*- Mitch Kronenberg, PhD*

# Landmark Discoveries Lead to **Brighter Futures**

The prolific discoveries from LJI are routinely published and cited in hundreds of prestigious scientific journals that span multiple therapeutic areas, including a host of "firsts" that elevated the Institute' s status as global leader in immunologic research.

Among them, LJI scientists were the first to reveal the structures of multiple families of viruses and the antibodies that can inactivate them; the first to demonstrate the role of autoimmunity in Parkinson's disease; and the first to prove the viability of a vaccine against heart disease. Since then, they have identified potential targets for leukemia and multiple targets for IgA nephropathy, an inflammatory kidney disorder.

Kyowa Kirin's drug discovery engine has produced equally important clinical advances on behalf of patients with unmet medical needs, and novel drug candidates are currently being evaluated in human trials around the world.

**"We get into this business to help patients. It's an incredible feeling that programs we've worked on at Kyowa Kirin are in the clinic and could potentially help patients."** *- Rachel Soloff, PhD*

# Advancing Novel **Drug Candidates**

More advances are on the horizon, with rocatinlimab—an anti-OX40 human monoclonal antibody—leading the way as a potential treatment for patients with moderate to severe atopic dermatitis.

Originally discovered at Oxford University, key insights into OX40's function were revealed by Mick Croft, PhD, at LJI, who identified its role in T cell differentiation, survival, and memory cell induction. Scientists at Kyowa Kirin generated and developed the antibody to target human OX40-expressing T cells and later advanced it into clinical trials.

Now, through a global partnership with Amgen, Kyowa Kirin is conducting eight Phase 3 trials in atopic dermatitis to investigate rocatinlimab's potential as the first and only T cell re-balancing therapy that inhibits and reduces pathogenic T cells. Additional clinical trials are planned for asthma, prurigo nodularis, and other conditions where T cell imbalance is the root cause of inflammation.

"The intellectual and technological expertise from LJI was instrumental in our early drug discovery research," said Rachel Soloff, PhD, Executive Director, Research Management at Kyowa Kirin.

## KEY DISCOVERIES

"In addition to OX-40 antibody, the partnership between LJI and Kyowa Kirin has yielded many results, including CD40 agonist antibody, light antibody, DR3, DCR3, and others," said Yoshifumi Torii, PhD, Vice President, Head of Global Research at Kyowa Kirin. "So I'm very hopeful that some of those projects will result in clinical proof of concept following the OX40 antibody."

*- Yoshifumi Torii, PhD*
*VP, Head of Global Research, Kyowa Kirin*

# Unraveling the Mysteries **of the Immune System**

Scientists at LJI and Kyowa Kirin are driven forward by the quest to more clearly understand the immune system and how to harness its untapped power to combat diseases.

"The immune system is involved in nearly every disease," said Saphire. "The daily role of the immune system is defending the body against cancer, heart disease, brain disease—every organ system within the body—and when immune system goes awry, inflammation and pain are universal."

Viruses are among the most cunning and stealthy opponents, continually shifting shape, masking themselves with sugars, and mutating faster than the immune system can detect them, a complex dynamic that LJI is striving to expose and overcome.

A prime example is Lassa fever, an Ebola—like virus in Africa that is particularly dangerous for pregnant women. While the virus is simpler in structure than HIV, the surface molecule shifts its shape and covers itself in sugars to hide from the immune system, complicating the creation of a vaccine. LJI is partnering with the WHO and CEPI to produce an effective vaccine.

"We're untangling it mechanistically in our lab, applying molecular engineering to shape the ideal immune response", Saphire said.

**"Luckily our immune system—and human intervention—can insert things, delete things, and change sequences; it has the remarkable ability to respond to things it hasn't seen before, to common colds and COVID. Sometimes, the right thing is really rare and really difficult to summon, and viruses escape or outpace antibodies."** *- Erica Sapphire, PhD, MBA*

# The **Future**

Today, that same inquisitive spirit is driving the team to pursue new modalities and classes of drugs that represent the wave of the future.

"Small molecules and antibodies have limited potential to have a curative effect", said Gunnar Kaufmann, PhD, Chief Scientific Officer at Kyowa Kirin. Cell and gene therapies offer the hope of a cure, and a deep understanding of immunology is essential to our success. This includes generating viruses and manipulating cells in order to investigate innovative drugs in preclinical studies. I think it's a wonderful opportunity to make a transformative change in the treatment of disease and in the lives of patients.

"LJI scientists can now engineer cells to amplify their activity in order to locate and destroy cancer cells, or to soften their activity and suppress autoimmunity and inflammation, noted Saphire. LJI scientists' combined expertise across dozens of subspecialties— cell metabolism, genomics, immunochemical circuits, computational immunology, and much more— enables them to modulate immune cells to achieve the precise immune function they want a patient to have."


**"For the first 30 years of our partnership, we tried to understand what the immune system was and how it worked and how the pieces fit together," said Saphire. "Now we're entering a whole new era; not just understanding how the immune system works, but using that information to control it for better health."**

# Partnering for **Patients**



# A Beautiful **Symbiosis**

As the partnership enters its 36th year, excitement for the future is palpable, and colleagues recount their experiences with deep admiration, affection, and appreciation.


***It's like a good marriage. The future is very bright for Kyowa Kirin and LJI, and everyone is committed to evolving our partnership; to embracing the scientific challenges and opportunities ahead and discovering life-changing therapies in the years to come.***

*- Gunnar Kaufmann, PhD*


***It's been a long, beautiful ride, and I'm looking forward to another 35 years right after this. Together we've discovered things that are actually helping improve human lives...***

*-Jeremy Young, MBA*

***"We're like family. It's a beautiful symbiotic relationship, and I think there's no other like it in the world. We're going in new directions. Because we have evolved for 35 years to perfectly fit and function together, we're going to find the most stunning new discoveries and ways to help patients and help people with our new focus and our new spirit.***

*- Erica Ollman Saphire, PhD, MBA*

# *Grateful for 35 Years of Shared Success*

On Behalf of Science, Patients, and the Future of Medicine

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