

amino scope®



KYOWA HAKKO BIO'S NEWS FROM AROUND THE GLOBE • WINTER 2018



An aerial photograph of a coastal industrial area. A river flows through the center, with a large industrial complex on the left bank featuring several tall smokestacks. The right bank is densely packed with industrial buildings, storage tanks, and a baseball field. In the background, a city and mountains are visible under a clear sky.

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Science Update

Special Seminar on Citrulline and Ornithine Sciences

Due to the rising interest in L-citrulline among academics and researchers, in 2008 Kyowa established a yearly seminar series on L-citrulline. In 2015, the topic of L-ornithine was added, and the seminar series is currently called “The Meeting of Citrulline and Ornithine Sciences”. The most recent meeting held in Japan on June 29, 2017 celebrated Kyowa’s tenth seminar on the topic. The 2017 meeting also coincided with the 20th anniversary of the Nobel Prize for research on nitric oxide (NO)—a significant event given that much current research on L-citrulline is tied to its role in NO production.

L-citrulline is not a constitutive amino acid in protein and exists as a free form in the body. L-citrulline acts as an NO producer in the vascular endothelium and contributes to maintain a healthy blood circulation. In terms of NO, endogenous NO was discovered in 1986 with Ignarro Ph.D., Murad Ph.D., and Furchgott, Ph.D. winning the 1998 Nobel Prize in Physiology or Medicine for their research on NO-cyclic GMP systems. This research has been continued by many researchers.

To celebrate the discovery of NO and to have academics and researchers recognize the importance of L-citrulline and its role in NO, Kyowa invited the Nobel prize winner, Louis Ignarro, Ph.D. (Professor Emeritus, Department of Molecular and Medical Pharmacology, UCLA School of Medicine) to present at the meeting.



Nobel prize winner, Dr. Ignarro, presents an overview of his research on nitric oxide at our Special Seminar on Citrulline and Ornithine Sciences.

Dr. Ignarro gave a special seminar titled “The Road to Stockholm: A novel mission nitric oxide as a unique signaling molecule in the cardiovascular system”, where he introduced his NO research and achievements to date.

Other topics and speakers at the seminar included: Metabolism and physiology of citrulline, presented by Masahiko Morita, Ph.D., Researcher, KYOWA HAKKO BIO., and Effect of citrulline on circulatory function, presented by Kunio Ishii, Ph.D., Professor, Center for Pharmaceutical Education, Faculty of Pharmacy, Yokohama University of Pharmacy. The seminar was co-chaired by Fumio Endo, M.D., Ph.D. (Hospital Director, Kumamoto Ezuko Ryoiku Iryo Center) and Toshio Hayashi, M.D., Ph.D. (Professor, Nagoya University Graduate School of Medicine, School of Health Sciences).

This year’s seminar was an extra special event with several notable academics both in attendance and as presenters meeting to discuss

research on L-citrulline. Kyowa would especially like to express great respect and gratitude to Dr. Ignarro for his significant contributions to NO research.

The Second Meeting of Glutathione Sciences

On September 29, 2017 Kyowa held its 2nd annual meeting on L-glutathione in Japan designed to help stimulate more interest in research among academics. The meeting offered a great opportunity to expand new physiological efficacy and scientific value for L-glutathione. Masahiko Morita, Ph.D., a researcher from KYOWA HAKKO BIO., opened the session with a presentation about the metabolic profiles and redox status of orally-administered glutathione in vivo. Other academics introduced new findings of the fundamental mechanisms and benefits of glutathione and its metabolites.

Specific presentations included: Cysteine supply systems prescribing glutathione biosynthesis,

presented by Sho Kobayashi, Ph.D., Department of Biochemistry and Molecular Biology, Graduate School of Medical Science, Yamagata University; Polysulfidated glutathione (GSSnH): its antioxidant, mitochondria respiration, energy metabolism, and sulfur stress in mammals, presented by Takaaki Akaike, Ph.D., Professor, Department of Environmental Health Sciences and Molecular Toxicology Tohoku University Graduate School of Medicine; and Reduced glutathione modulates differently the intracellular trafficking of melanocyte-specific proteins, which results in the attenuation of melanization, Genji Imokawa, Ph.D. Professor, Utsunomiya University, Center for Bioscience Research & Education.

Twenty-one Japanese academics attended the meetings and discussed their topics enthusiastically. The meeting was co-chaired by Junichi Fujii, Ph.D., Professor, Department of Biochemistry and Molecular Biology, Graduate School of Medical Science, Yamagata University, and Hideyo Sato, Ph.D., Professor, Department of Medical Technology, Faculty of Medicine, Niigata University.

Kyowa has decided that it will continue holding these meetings to provide an opportunity to discuss the meaning of glutathione administration with academics, and plans on expanding the activities internationally in the future.



Twenty-one Japanese academics attended the Meeting of Glutathione Sciences

Research on Glutathione for Protecting the Intestinal Mucosa

Kyowa and Josai University in Japan joined in an animal study titled "Protective effects of oral glutathione on fasting-induced intestinal atrophy through oxidative stress" that has been recently published in the World Journal of Gastroenterology¹. The results show oral glutathione administration during fasting reduces reactive oxygen species (ROS) and enterocyte apoptosis, and enhances cell proliferation in the rat jejunum.

Glutathione is the most abundant antioxidant in the body and protects the tissues from ROS damages. Regarding intestinal mucosa, glutathione sources are mainly hepatic glutathione from biliary secretion² and dietary glutathione from various foods³. However, fasting and other states of malnutrition restrict to supply glutathione to the body and influence intracellular glutathione status. It is reported that the small intestine and hepatic glutathione concentration in rats fall 53% and 69% respectively following 24 h food restriction⁴.

Fasting for 2-3 days causes intestinal mucosal atrophy and increases ROS production following activation of inducible nitric oxide synthase (iNOS) expression⁵. In this study, rats received 50 or 500 mg/kg body weight/day of glutathione orally at 24, 48, and 72 h before and after fasting. The jejunum mucosa damages and ROS levels were evaluated after 48 or 72 h fasting. Glutathione treated animals improved jejunal mucosal height (Fig. 1), and suppressed the inflammatory response, such as iNOS expression and oxidative damages compared to saline (SA) treated controls.

This study showed that oral glutathione acts to reduce ROS generation in the intestinal lumen and enhances intestinal cell proliferation (Fig. 2), which could lead to a possible role of glutathione for protecting gut barrier function.

The digestive health market is growing and estimated at US\$1 billion dollars according to SPINS data. The argument about the bioavailability of oral glutathione has often been discussed. However, Kyowa's recent study suggests that oral glutathione contributes to the protection of intestinal mucosa before the absorption into blood. This study shows a new side of glutathione's effects and suggests that it has potential as both a dietary supplement and medical food for supporting digestive health.

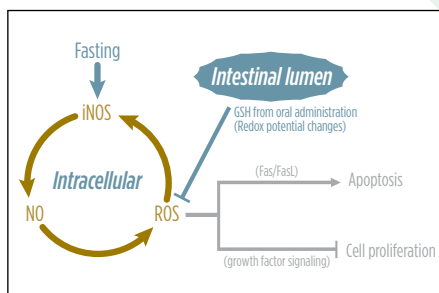


Fig. 1) Schematic diagram of oral glutathione for protecting the intestinal mucosa

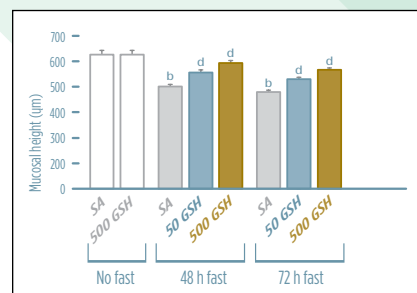


Fig. 2) Effect of fasting and glutathione treatment on jejunal mucosal atrophy.

Values represent the mean \pm SE. b $P < 0.01$ vs the normally fed control. d $P < 0.01$ vs the respective SA-treated group in each fasting period. 7-8 rats were tested in each group. GSH: Glutathione; SA: Saline.

Reference:

- 1) Uchida H et al., World J Gastroenterol., 23(36):6650-6664, 2017.
- 2) Aw TY., J Clin Invest. 94(3):1218-25, 1994.
- 3) Jones DP, et al., Nutr Cancer., 17(1):57-75, 1992.
- 4) Kelly FJ., Br J Nutr. 69(2):589-96, 1993.
- 5) Ito J. et al., Am J Physiol Gastrointest Liver Physiol., 298(6):G916-26, 2010.

Product News

Patent on Setria® for enhancing immunity established in the EU

Glutathione is the most abundant antioxidant and is also essential for immune function in the body.

Kyowa did a joint study with Penn State University College of Medicine to determine the effects of oral Setria glutathione supplementation on glutathione levels and regulation of certain immunological functions¹⁾ and filed an international patent application based on the studies results. A patent on a method to enhance immunity by glutathione

intake has recently been granted in the EU. In this patent, Kyowa claims that “non-therapeutic oral use of glutathione or salt thereof for enhancing immune function wherein the agent is to be administered for 3 months or more.”

The maintenance of glutathione levels in the body is important to staying healthy. However, aging²⁾, drinking alcohol³⁾ and other various factors induce a decrease in glutathione levels. Glutathione depletion impairs immunity function, leading to an increased susceptibility to infection such as influenza⁴⁾.

Previous studies showed that glutathione inhibits virus proliferation dose-dependently in vitro and oral glutathione has an anti-influenza activity in vivo⁵⁾.

Kyowa's collaborative clinical study with Penn State University College of Medicine reported that blood glutathione levels significantly increase from baseline after 1, 3 and 6 months by oral Setria 250mg and 1000mg/day (Fig 1). After 1 month of washout period, blood glutathione levels returned to baseline. Regarding immune parameters, lymphocyte proliferation and NK cell

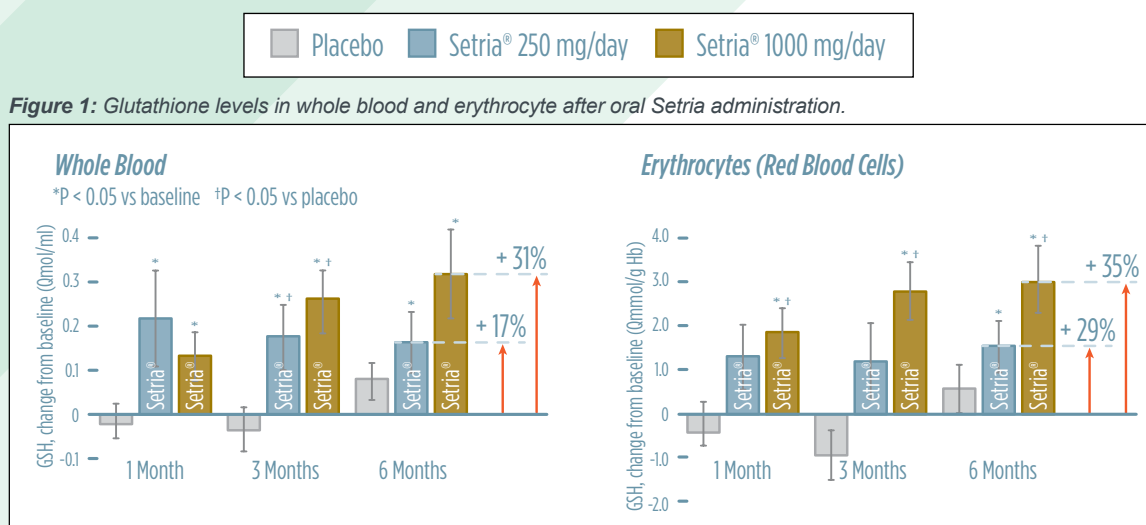
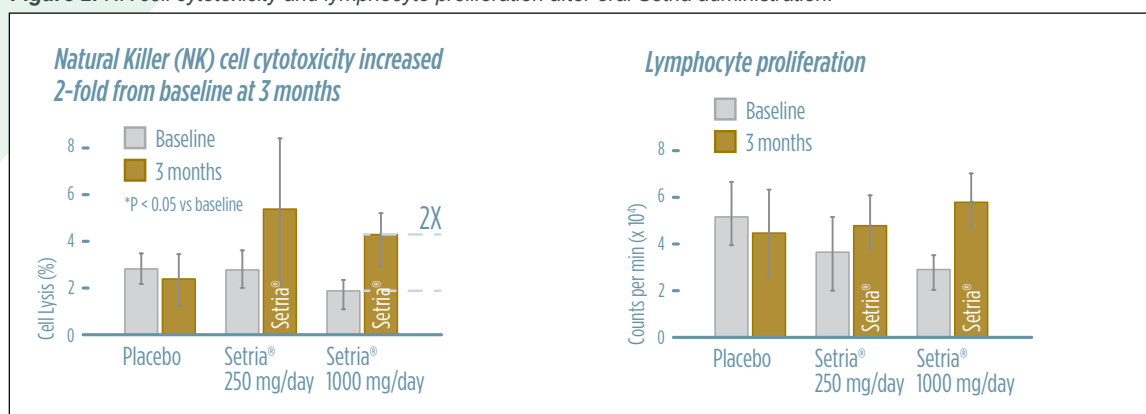


Figure 2: NK cell cytotoxicity and lymphocyte proliferation after oral Setria administration.





Sports Nutrition and Wellness workshop in Johannesburg, South Africa

cytotoxicity increased after 3 months of oral Setria® supplementation in healthy subjects (Fig 2). Comprising 10-15% of circulating lymphocyte pool, NK cells are large granular lymphocytes of the innate immune system and the decline in NK cell function is accompanied by human ageing⁶). Therefore, it is suggested that oral Setria® glutathione every day helps keeps high levels of glutathione and acts as not only an antioxidant but also a booster of immune function in healthy subjects, especially older adults.

Reference:

- 1) Richie JP et al., *European Journal of Nutrition*. 54(2): 251-63, 2015.
- 2) Van Lieshout MM and Peters WH. *Carcinogenesis*. 19(10): 1873-5, 1998.
- 3) Videla LA and Valenzuela A. *Life Sci*. 31(22): 2395-407, 1982.
- 4) Ghezzi P. *International Journal of Natural Medicine*. 4: 105-113, 2011.
- 5) Cai J et al., *Free Radical Biology & Medicine*. 34(7): 928-36, 2003.
- 6) Hazeldine J and Lord JM. *Ageing Res Rev*. 12(4): 1069-78, 2013.

Introducing Kyowa to the South African Market

This November, Kyowa Hakko Bio Italia (KHIT) together with its partner Sumitomo Corp., held a first ever Sports Nutrition and Wellness workshop in Johannesburg, South Africa.

The purpose of the workshop was to bring together manufacturers, formulators, R & D and sales executives in sports nutrition, dietary supplements and wellness, to explore and help them capitalize on the opportunities in this fast-growing market segment.

Kyowa's European team presented an overview of nutrition market trends, the benefits and science of branded ingredients and how they compliment current market opportunities, plus Kyowa's marketing activities and support for its channel partners. Masaki Maeda, Strategy Manager at KHIT introduced the

participants of the workshop to the essence of Kyowa's proprietary manufacturing processes and quality control standards.

Nicola Urso, Vice President of KHIT commented: "We are very pleased with the feedback and response we have got from those that attended and we have already had a number of enquiries for additional information and requests for product samples. Because of its geographical location South Africa is a challenging market for us so this format of event is a great way to bring people together and to be able to introduce Kyowa, our science and innovative products."

BioKyowa

BioKyowa is Kyowa Hakko Bio's U.S. based amino acid production facility in Cape Girardeau, Missouri, and many visitors have asked how the plant came to be located there. When the facility started operation in 1984, the first product produced was L-lysine—an ingredient used mainly in animal feed. The plant location was selected based on four factors. First was proximity to its primary customers which at that time were swine and chicken producers located in the Midwestern United States. Second was the plant's location at the edge of the U.S. corn belt. Corn syrup is the main sugar source for BioKyowa's fermentation process and there are numerous corn syrup plants located within a reasonable transportation distance from Cape Girardeau. Third was its proximity to the Mississippi River, because in 1984, some raw materials were delivered by barge to a nearby river terminal. The fourth factor was low cost electricity because utility costs are significant in a high-volume aerobic fermentation facility.

Over the years, BioKyowa has evolved from a dedicated animal feed amino acid producer to a

facility that produces thirteen different amino acids for customers worldwide in the food, pharmaceutical and industrial sectors. Production of L-lysine for animal feed ended in June 2002, but the facility's proximity to corn syrup suppliers and low cost of electricity are still valid factors for BioKyowa's location.

As one of the larger industrial employers in Cape Girardeau, BioKyowa has been involved in many community events over the years. Support of the local Chamber of Commerce

and United Way, conducting blood drives for the Red Cross, conducting fund raisers for the Salvation Army, and most recently raising money for the victims of hurricanes Harvey, Irma and Maria are just some of the activities that BioKyowa has been involved with.

Located approximately 115 miles southeast of St. Louis, many people may have seen Cape Girardeau and not realized it. The 2014 psychological thriller movie *Gone Girl* was filmed in Cape Girardeau with many scenes taking place in The Bar located in the downtown area. The Bar is only a few blocks away from a 15-foot high floodwall that protects the city from Mississippi River flooding. Covering the floodwall is an 18,000 square foot mural with 24 panels depicting the history of the area. Many other local venues were used in the movie including the Bill Emerson bridge which crosses the Mississippi River at Cape Girardeau. BioKyowa has also had a few famous visitors over the years, including Missouri Governor Jay Nixon in 2011.



Cape Girardeau flood wall mural



BioKyowa supports the United Way in Cape Girardeau

Marketing News

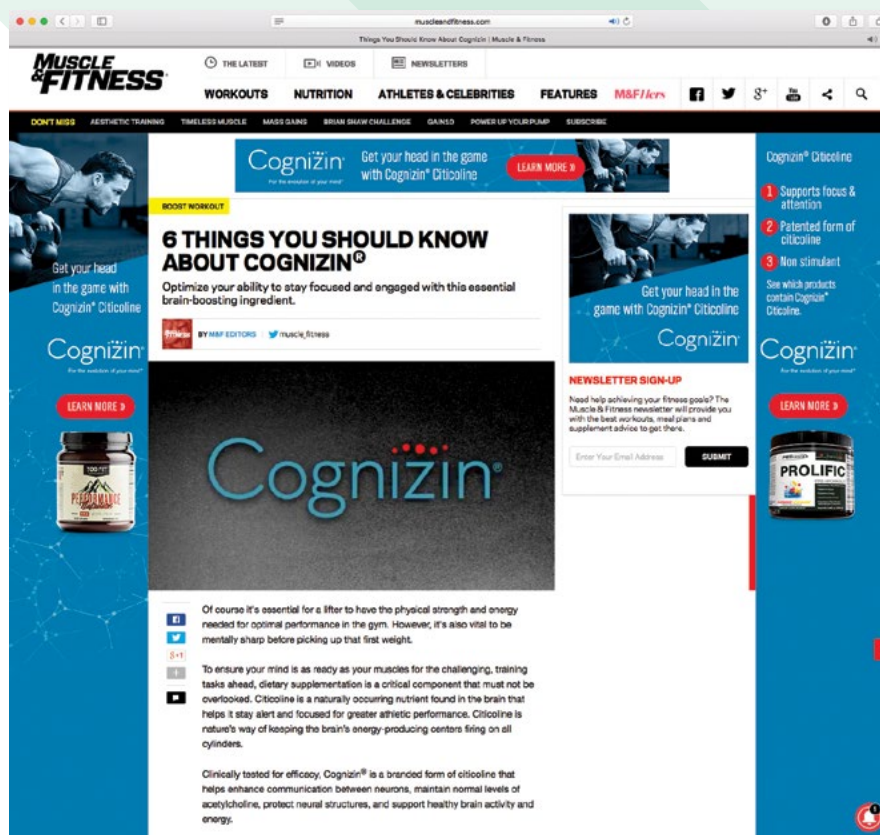
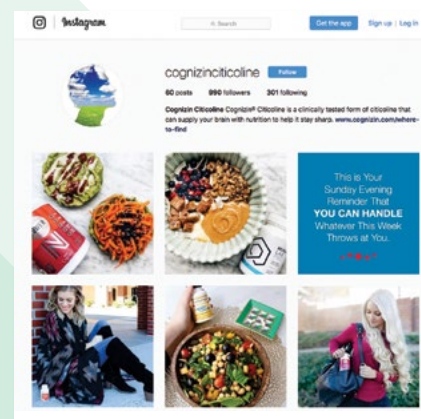
The latest BUZZ on Cognizin®

The brain health market is booming in the U.S. as well as in many other developed countries and shows no signs of slowing down. The rising cost of health care and an increasing aging population is a huge factor, but many young people who may be feeling overwhelmed with all the responsibilities of modern life are also showing an increased interest in nutritional support that can help them stay sharp and focused.

Kyowa's Cognizin® Citicoline is perfectly positioned to address consumer concerns and needs for brain health. A clinically studied ingredient that supports claims of increased focus and attention, Cognizin is also 100 % pure, vegetarian, allergen-free and Kosher. Cognizin is also a non-stimulant ingredient.

Recent online media coverage creating awareness of Cognizin's brain health benefits includes a post in the very popular lifestyle blog *POPSUGAR* that boasts upward of 2.9 Billion annual pageviews. Additionally, *Muscle & Fitness* Digital is currently hosting an article + video about Cognizin's focus and attention benefits that can be beneficial to anyone wanting to keep "their head in the game". *Muscle & Fitness* Digital has an audience of 8 Million viewers per month.

Social media is also growing and an important tool in the marketing mix helping to increase awareness. Cognizin currently has 990 followers on Instagram and 12,327 likes on Facebook.



Help your brain keep up

Modern life is complicated. Between work, kids, aging parents and home repairs, your brain's energy stores are constantly drained. Re-energize it with Cognizin® Citicoline. Backed by years of clinical trials, Cognizin increases ATP energy in brain cells and helps protect aging neurons from free radical damage.* You ask a lot of your brain. Give it the energy, nourishment and protection it needs with Cognizin.*

Cognizin®

For the evolution of your mind®

Train-your-brain games at
www.cognizin.com



*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Look for Cognizin® Citicoline in these fine brands.

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Tradeshows & Conferences

Fi India & Hi 2017

Kyowa Hakko Bio India participated for the first time in Fi India & Hi 2017 held November 9-11 at the Bombay Convention & Exhibition Centre in Mumbai. As a growing market for the Nutraceutical Industry, India is becoming more regulated by the Food Safety And Standards Authority of India (FSSAI) an organization covering health supplements, nutraceuticals, food for special dietary use and special medical purpose, functional foods and novel foods.

The reason to attend the exhibition was to create more awareness for Kyowa's branded ingredients like Setra[®], Cognizin[®], Aquagluta[®], Sustamine[®] and Kyowa Quality[®] amino acids. The response for Setria[®] Glutathione was very good with many inquiries for skin whitening and dietary applications. The interest in Cognizin[®] for brain health and attention was also good. The event was very successful as over 100 plus visitors from various industries such as pharmaceutical, nutraceutical and health food visited our booth and had a fruitful meeting.

A New Look for Kyowa at SupplySide West

Kyowa USA unveiled its new booth at this year's SupplySide West 2017 in Las Vegas. The updated booth design showcases Kyowa's key branded ingredients and provides ample meeting space for existing customers and new guests. The clean, modern look of the booth contributes to Kyowa's brand image as a top-quality manufacturer with products that are a perfect fit for many of today's lifestyle concerns.



Upcoming Events



February 14-15, 2018
Madrid, Spain



February 22-24, 2018
New York, NY USA

Nutrition in Athlete Development Summit

March 1-2, 2018
Madrid, Spain



March 9-11, 2018
Anaheim, CA USA



April 10-11, 2018
Secaucus, NJ USA



May 2, 2018
Sydney, Australia



May 15-17, 2018
Geneva, Switzerland



June 7-9, 2018
Clearwater Beach, FL USA



June 26-July 1, 2018
Denver, CO USA



July 15-18, 2018
Chicago, IL USA



Japan—Headquarters

Kyowa Hakko Bio Co., Ltd.

North & South America

Kyowa Hakko USA

Europe

Kyowa Hakko Europe GmbH

Kyowa Hakko Bio Italia S.R.L.

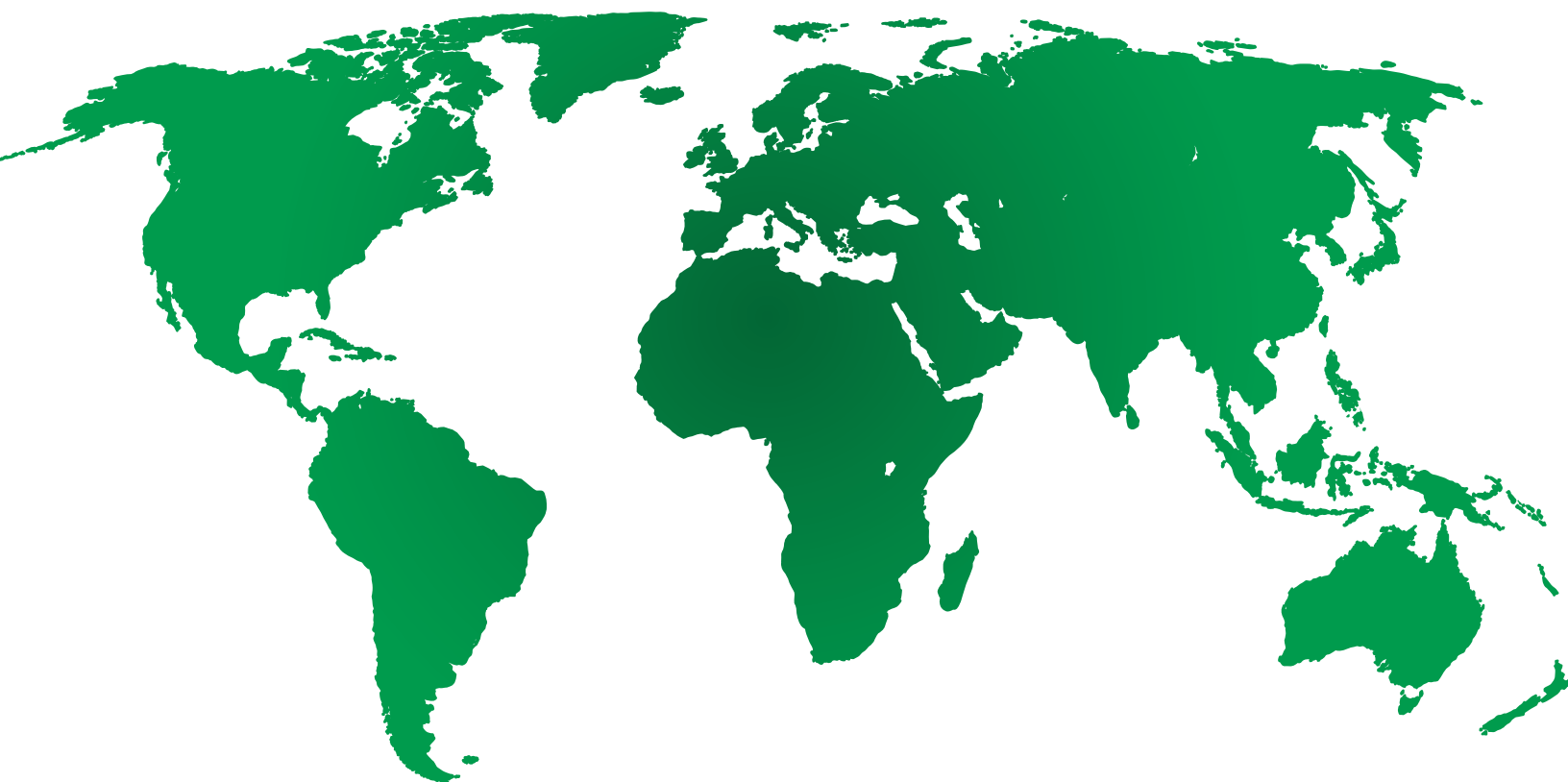
China & South East Asia

APEC (except Japan)

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