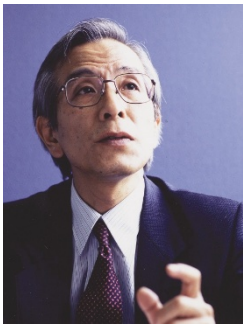
Topping the list of scientists who have published the greatest number of 'hot papers' over the past two years according to the ISI citation index, are Kenji Kangawa and Masayasu Kojima. The ranking system is based on manuscripts that are cited at an unusually high rate for their field. In Kangawa and Kojima's case, it is the discovery of a hormone related to feeding and obesity that has attracted so much attention.

Kenji Kangawa and Masayasu Kojima

Kenji Kangawa and Masayasu Kojima met at Miyazaki Medical College in 1983. Kojima was a newly minted medical student and Kangawa was an assistant professor of some international standing—the previous year he had isolated atrial natriuretic peptide (ANP) from the human heart, a hormone with potent natriuretic, diuretic and vasodilatory properties, which reveals that the heart is not only a pump, but also an endocrine organ.



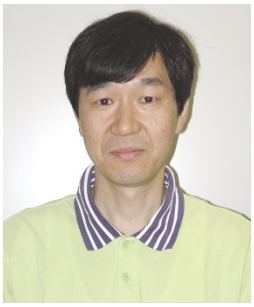
Hormone hunters

Japanese laboratories such as the Miyazaki Department of Biochemistry and the National Cardiovascular (NCVC), to where Kangawa and Kojima transferred their operations a decade later, make Japan quite simply "the best place [in the world] to work in the field of bioactive peptides," says Kangawa. And who could argue with that. Tomoh Masaki of Kyoto University identified endothelin, and Masahiko Fujino of the Takeda Pharmaceutical company has characterized several ligands for orphan receptors. Kangawa's mentor, Hisayuki Matsuo, discovered luteinizing hormone- releasing hormone (LHRH). And in addition to ANP, Kangawa himself has determined the chemical structure of more than 50 bioactive peptides including brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP).

Not long after Kangawa moved to the NCVC at Osaka, he isolated adrenomedullin. At the same time, G protein–coupled receptors were being reported in the literature, including the growth hormone secretagogue receptor (GHSr), which was discovered by a team at the pharmaceutical company, Merck. Kangawa's group redirected efforts to finding the endogenous ligand for GHSr. By applying his molecular biology experience, Kojima developed a new assay through which to isolate the ligand: a CHO cell line expressing GHSr in which changes in the second messenger, intracellular calcium, can be monitored.

The popular notion was that the ligand to GHSr was produced in the hypothalamus; so investigators the world over were frantically testing brain extracts. "But all our studies were in vain," remembers Kangawa, "and there were three possible explanations for the failure. Either there was no ligand in the brain; it was in the brain, but in such small amounts that it could not be detected; or it was so unstable that we could not isolate it."

His experience with the brain peptides BNP and CNP told him that the third option was unlikely, and without then knowing the role that GHSr-ligand plays in the stimulation of feeding, his team began to sift through peripheral tissues for the evasive ligand. Before long, one experiment involved assaying gut tissue. "If Merck had searched the stomach, they would have discovered ghrelin before us," admits Kangawa. But it was his training in organic chemistry that gave him the edge and he recognized the existence of a 28-amino-acid peptide from the gut with an unusual fatty-acid modification, an *N*-octanoyl modification at its third serine residue: ghrelin was the ligand for the GHSr and it was synthesized in vast amounts in the stomach.



Hormone hunters

Production of ghrelin is triggered by fasting and cachexia, while its concentration decreases in obesity indicating that it is involved in the regulation of energy balance. It also enables the stimulation of growth hormone release from the anterior pituitary gland. Given that it has such a wide range of physiological functions, it is not surprising that since its discovery in 1999, ghrelin has been the subject of more than 130 research articles, over 40 of which are co-authored by Kangawa.

Although Kangawa and Kojima have active research collaborations in the US, UK, Denmark, Spain and other European countries, neither scientist has worked outside Japan. Early in his career, Kangawa went to the US "as a trial" for doing a post-doc period abroad. But he returned to Miyazaki after only one month and insists, "If I had stayed in the US, I could not have identified ANP."

While Kojima also believes that the Miyazaki lab is a leader in purifying and analyzing peptide hormones, he is not entirely happy with the overarching approach to biomedical research in Japan, particularly now that he is a seasoned investigator. "Last year the government announced a policy to produce 50 Nobel Laureates within next 30 years, and also multiplied research grants for scientists under the age of 39. It's true that a great many advances in science tend to be made by young researchers, but I'd like the government to evaluate us not based on age but on the work we've done." Kojima is also perturbed by the government's fixation on commercially applicable research, and says one of his dreams is to run his own lab in foreign country.

But that dream is on hold, at least for now. Last year, after working together successfully for 18 years, Kojima moved to Kurume University to start up his own lab, where he is now hunting for novel hormones. Meanwhile, Kangawa's lab at the NCVC is investigating the effects of ghrelin on the cardiovascular system, in particular its role in chronic heart failure, dilated cardiomyopathy and cardiac cachexia. And he has begun investigation of ghrelin's potential clinical value for cachexia in cancer and anorexia. His prowess at identifying new molecules continues unabated—he has recently submitted data on a novel hormone to a journal for publication.

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