

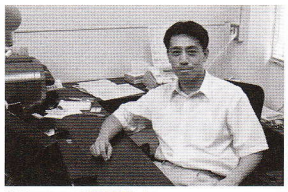


Comprehensive pharmaceutical sciences

Meet four members of the Graduate School of Pharmaceutical Sciences at Osaka University, all of whom are devoted to the comprehensive analysis of chemical substances that can impact our lives. Like other scientists in the school, these four have devised technologies that have opened new ways of seeing chemical-based phenomena, thus helping to keep Japan at the forefront of pharmaceutical sciences.

Applied biopharmaceutical sciences

Akemichi Baba has his own perspective on finding treatments for psychiatric disorders. Such disorders are complex, and those researching treatments have a hard time knowing where to start. Baba has provided a solid foundation.

He has spent nearly two decades characterizing pituitary adenylate cyclase activating peptide (PACAP), a polypeptide first isolated in 1989 and known to play an important role in the cAMP pathway. Baba and his team of researchers soon took the lead in examining PACAP by cloning it, carrying out genomic analyses, identifying its receptors, tracing its involvement in molecular pathways and localizing its distribution. It turns out that the peptide is mainly expressed in the brain — an exciting finding that suggested a potentially important role in brain function.

That interpretation turned out to be correct. Using modern gene-targeting methods, Baba's team found that when the PACAP gene was knocked out, mice suffered the tell-tale signs of schizophrenia: hyperactivity, reduced ability to adjust to disturbances (lower pre-pulse inhibition), a tendency to jump around explosively, cognitive dysfunction and depression-like behaviour.

It was a triumph of 'reverse pharmacology', an approach in which scientists study phenotypic effects of a disturbance to a complex system. Baba knows that the phenotypic expression of genes also depends on certain environments, so he has also been studying relevant environmental factors.

Baba's PACAP knockout mouse is on its way to becoming a new model for human schizophrenia. The mice show improvement when given anti-psychotics. And analogies with humans are supported by the fact that a certain mutation in the PACAP gene, found to be significant in schizophrenic patients, is associated with smaller hippocampal volume and poor memory.

What causes schizophrenia and how should it best be treated? With his mice, Baba is on his way to finding out.

Molecular pharmaceutical sciences

Hiroyuki Mizuguchi is perfecting methods for introducing genes into cells at will — a technology that offers the unprecedented ability to manipulate cells for biomedical research — to produce vectors for gene therapy and potentially to carry out life-saving clinical therapies. Adenovirus vectors accomplish this feat, with the added advantage that they express the gene of choice without disturbing the host's DNA. But conventional adenovirus vectors also have problems, such as being unable to penetrate cells that lack a certain type of receptor. Mizuguchi has experience in solving such tough problems.

"We want to find a way to take advantage of the merits, limit the problems and find a new generation of adenovirus vectors that can serve even more functions," says Mizuguchi.

Mizuguchi pioneered an efficient way to make adenovirus vectors through a patented approach that is now commonly used worldwide. And with several publications and patents on a new kind of adenovirus vector, he is well positioned to make even more breakthroughs.

Bioorganic pharmaceutical sciences

Satoshi Obika found a recipe that works. Twelve years ago, he pioneered a technology that stabilizes nucleic acids, whether DNA or RNA, by adding an extra bridge in the molecule's sugar.

The 'bridged' nucleic acid (BNA) outdid his expectations, binding to complementary RNA with an affinity more than 100,000 times that of normal DNA. "I was very surprised," says Obika.

BNA can be used to increase the specificity of detection in common DNA microarrays or polymerase chain reactions. The specificity will also allow 'antisense' blocking of DNA transcription or RNA translation, which could make DNA-based clinical therapies possible. Obika designs a successful BNA roughly once per year, each with its own RNA or DNA targets, paving the way to a future full of discoveries.

Environmental pharmaceutical sciences

Yasuo Tsutsumi, a toxicologist, thinks people should be worrying more about the smaller things, and his animal studies back up that position.

He studies silica materials composed of molecules smaller than 100 nanometres in diameter, which are increasingly being used in cosmetics, food and drugs. His first question: do they get into the body? The answer he found in his mouse and pig studies is 'yes' — even when applied to the skin, which is supposed to be the toughest barrier to pass. The second: where do these nanoparticles go in the body? The answer: into many vital organs, including the brain. The last question: are they safe? "We don't know yet," says Tsutsumi, "which is exactly why we have to extend our studies on nanotoxicology as quickly as possible."

Tsutsumi wants to bring these facts to our attention. "We believe these products are safe, without any evidence," he says. "I want to grasp the risk involved."

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