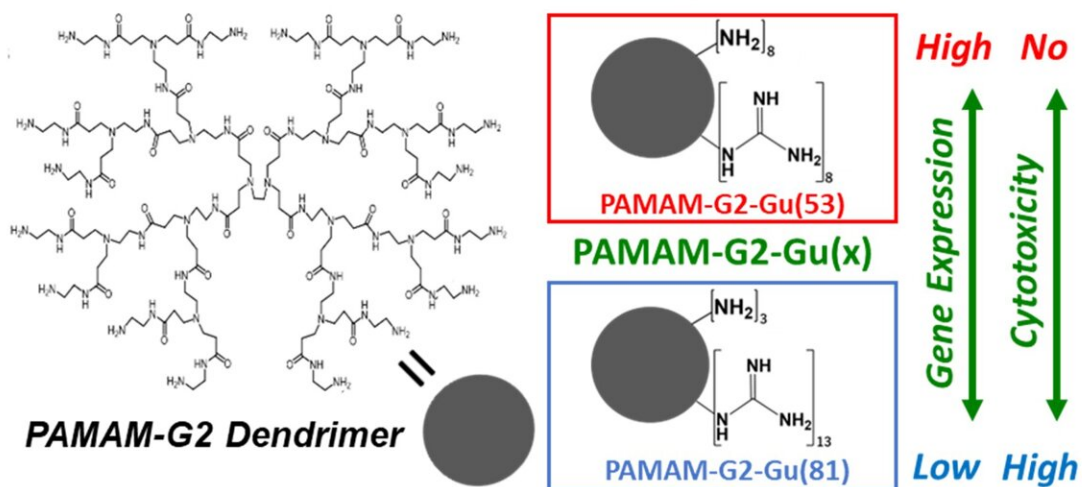
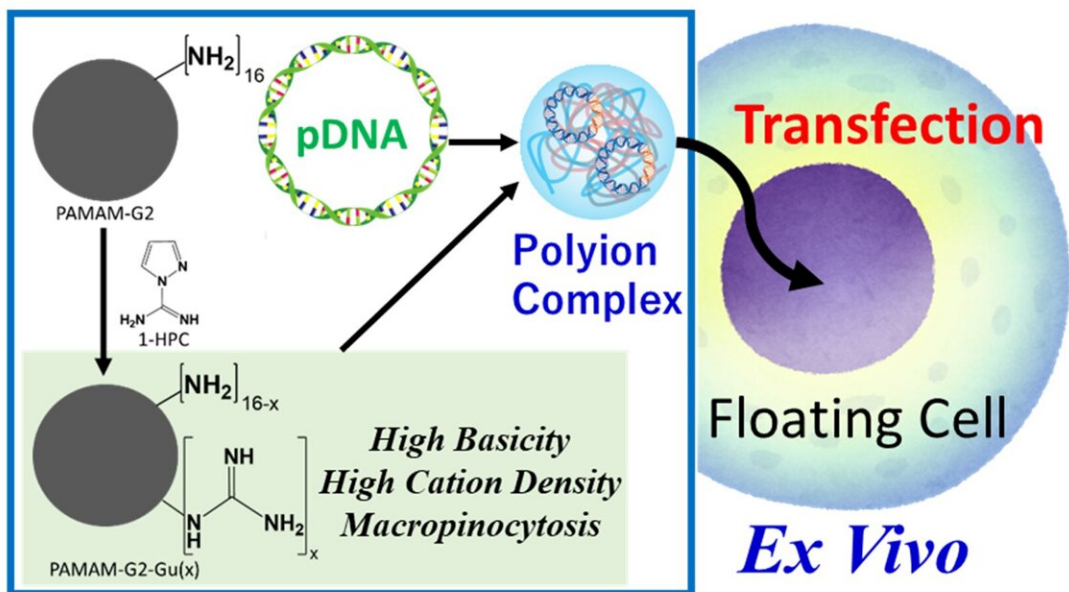


# Hairy polymer balls help get genetic blueprints inside T-cells for blood cancer therapy

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DNA is bound onto polyion complexes before being transported into floating cells. PAMAM-G2 dendrimer molecules may be modified by guanidine groups to produce, highly charged structures which can realize excellent gene transport and low cytotoxicity with the right proportion of guanidine. Credit: Tokyo Metropolitan University

Scientists from Tokyo Metropolitan University have realized a new polymer that can effectively transport plasmid DNA into T-cells during chimeric antigen receptor (CAR) T-cell therapy, a key treatment for blood cancer. Importantly, it can get genes into floating T-cells, not only ones fixed to surfaces. It is stable, non-toxic, and doesn't use viruses. It outperforms polyion compounds considered a gold standard in the field, paving the way for new therapies.

Their research is published in the journal *Polymers for Advanced Technologies*.

T-cells, or lymphocytes, are a type of white blood cell that helps our immune system fight germs and protect us from disease. Recently, technology has become available that helps reprogram T-cells to fight cancer. Chimeric antigen receptor (CAR) T-cell therapy works by introducing new genes into T-cells; these new "instructions" help create receptors on the [cell surface](#) which can bind to cancer cells, effectively making cancer cells a prime target for our own immune systems.

The key step in the process is effectively delivering DNA, the genetic blueprint, into T-cells taken from a patient, in a process known as ex-vivo transfection. Many methods use viruses, which are naturally good at delivering genes. However, this has its own set of problems, as there are

safety concerns around the viruses themselves, and our immune system might attack them outright. That is why researchers are turning to alternative means, specifically polyion complex (PICs), where large polymer structures bind DNA and help carry it into T-cells. However, PICs are known to only be able to get genes into T-cells bound to surfaces, not floating around as they would in a normal sample.

Now, a team led by Professor Shoichiro Asayama from Tokyo Metropolitan University have created a new polymer compound that can effectively get plasmid DNA (pDNA) into floating T-cells. They used a dendrimer, large polymers with a branching structure that resembles a hairy ball.

Specifically, they used a second generation polyamidoamine (PAMAM-G2); second generation, in this case, refers to the number of times new branches are formed going out from the central structure. Experimenting with modifications to the ends of the branches, they found that they could realize a wide range of binding behavior of pDNA to PAMAM-G2.

In particular, the team found that PAMAM-G2 with a specific ratio of primary amine groups at the ends of branches replaced by highly basic guanidine (Gu) groups produced excellent carriers for pDNA. PAMAM-G2-Gu had a very high charge and were the right size for macropinocytosis, a common mechanism whereby cells "swallow" and incorporate outside material.

With the right recipe, the PICs were also non-toxic and stable in blood plasma. Crucially, PAMAM-G2-Gu(53) (53% replacement by guanidine) significantly out-performed branched poly(ethylenimine) or bPEI, a gold standard PIC for gene transfection, in tests on floating T-cells.

Given their low toxicity and outstanding carrier properties, the team believe they have a viable candidate for ex-vivo transfection in the next generation of CAR T-cell treatments, a crucial therapy option for sufferers of a wide range of life-threatening illnesses.

**More information:** Ryoto Kon et al, Synthesis of guanidinium-dendrimer-type pDNA carriers for gene delivery into floating blood cells, *Polymers for Advanced Technologies* (2023). [DOI: 10.1002/pat.6136](https://doi.org/10.1002/pat.6136)

Provided by Tokyo Metropolitan University

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