Dendrimers: The tiny tentacles shown to evade our immune response

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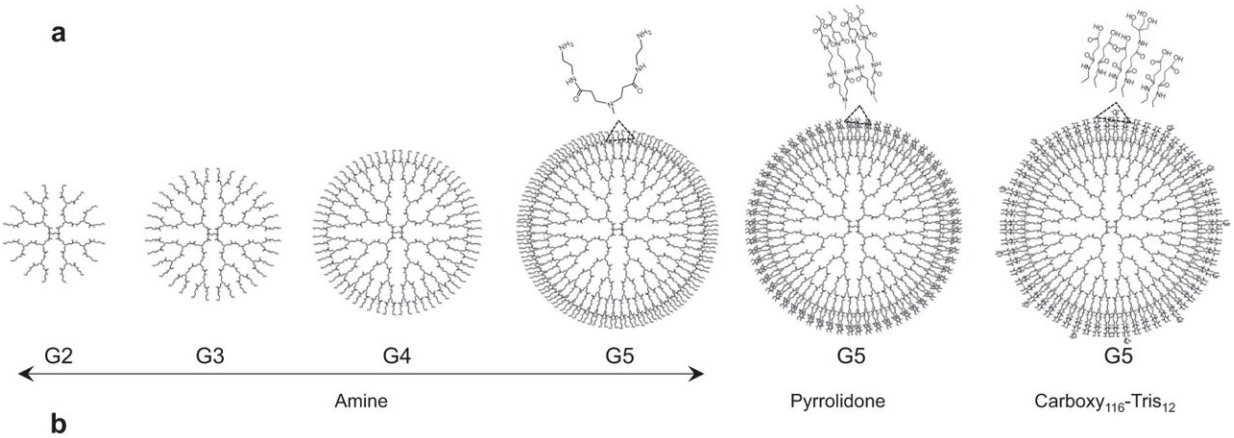

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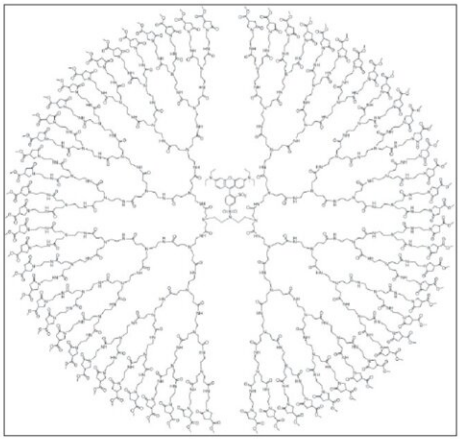
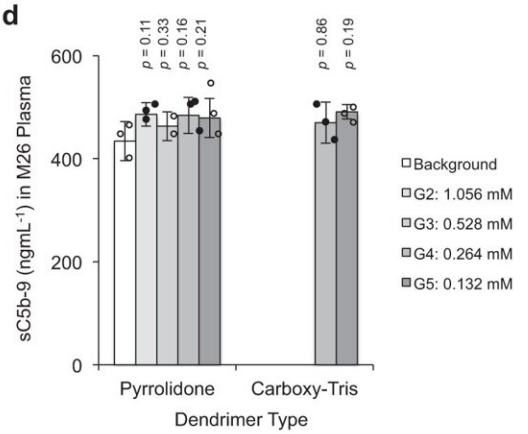
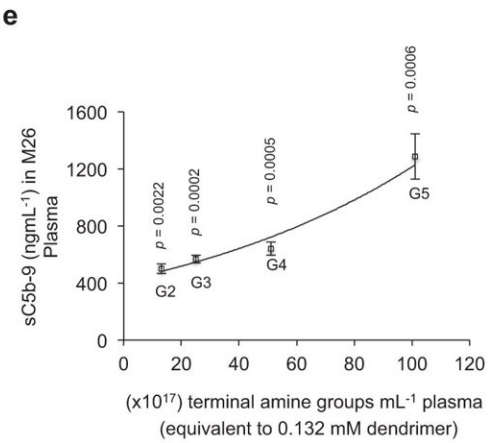


c

Dendrimer	Molecular mass ($gmol^{-1}$)	Number of terminal groups	Radius of gyration (Å)* (amine-terminated only)
G2	Amine 3284.2 Pyrrolidone 5302.0	16 16	not available
G3	Amine 6936.9 Pyrrolidone 10972.4	32 32	15.8
G4	Amine 14242.5 Pyrrolidine 22313.6 Carboxy-Tris 21233.5	64 64 58-6	17.1
G5	Amine 28853.1 Pyrrolidine 44996.0 Carboxy-Tris 43620.1	128 128 116-12	24.1





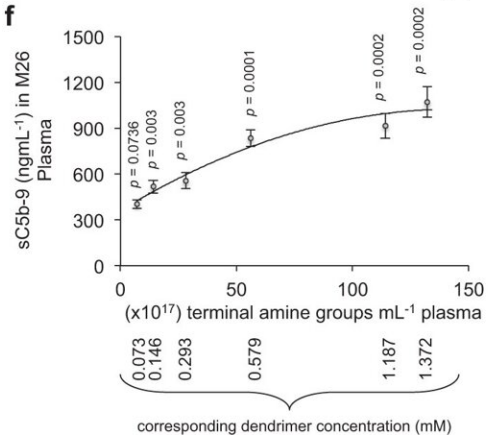


Fig. 1: Dendrimer characteristics and the role of dendrimer end-terminal functionality in complement activation. **a** Structural representation of G2–G5 dendrimers with magnified views of the highlighted end-terminal region (dashed triangles). At physiological pH the end-terminal primary amines and carboxylic acids are predominantly protonated and deprotonated, respectively. **b** Typical structure of a G4 PAMAM dendrimer with a precisely core positioned sulforhodamine B. **c** Selected properties of G2–G5 dendrimers. *The values for radius of gyration were adopted from a previous small-angle X-ray scattering study26 **d** Pyrrolidone- and carboxy-Tris-terminated dendrimers do not trigger complement activation in human plasma (plasma code, M26; a healthy individual Caucasian, male, 26 years old) as determined through measurements of sC5b-9. Complement activation is compared at an equivalent number of dendrimer terminal groups (101 × 1017 terminal groups per mL of plasma). **e** The effect of different generations (G2–G5) of amine-terminated dendrimers on generation of fluid-phase sC5b-9 in M26 plasma. The best coefficient of correlation (R2 = 0.965) is computationally defined by the equation y = 422.15e0.0106x. **f** The effect of G2 dendrimer concentration on sC5b-9 formation in M26 plasma. The best coefficient of correlation (R2 = 0.955) is computationally defined by a quadratic polynomial fit (y = –0.0319x2 + 0.2006x + 366.92). In e and f, mean background sC5b-9 levels were 367 ± 7.2 μgmL−1 and 361 ± 7.3 μgmL−1, respectively. In panel d, bars represent mean ± s.d. of three separate experiments and each dot indicates the mean of three technical replicates. In e and f, each point represents the mean ± s.d. of three separate experiments, and each experiment was done in triplicate samples. In d, e and f, p values (unpaired, two-sided) are compared with the respective background (control) incubation. Credit: DOI: 10.1038/s41467-021-24960-6

Tiny synthetic particles known as dendrimers avoid detection by our immune system and could help develop a new way to deliver drugs into the body without triggering a reaction.

The new research led by Professor Moein Moghimi, Professor of Pharmaceutics and Nanomedicine at the School of Pharmacy, Newcastle University, UK, in collaboration with international colleagues is published in *Nature Communications* alongside an accompanying blog.

The dendrimer is a chemically-created molecule with tentacles branching out in a highly-symmetrical structure around a central core. The research describes how dendrimer tentacles arranged incredibly closely to each other—less than one nanometer apart—avoided detection by the complement system, part of our immune system.

Our immune system is equipped with many tools to recognize and eliminate invaders. For example, our blood contains sensors belonging to a family of defense system known as the "complement system," which recognizes unique patterns expressed by invaders such as bacteria and viruses. Binding of these sensors to pathogens alarms the immune system and triggers an immune response. These sensors are termed "complement pattern-recognition (CPR)" molecules.

CPR can sense surface patterns that are regularly repeated so close to each other, for instance in 2–15 nanometer ranges—a distance, which is at least 5000 times thinner than the thickness of a typical sheet of paper.

The international team discovered however, that the CPR could not sense patterns repeated closer to each other, for instance, at 1 nanometer or less.

At a nanoscale level, the team grew tiny particles known as dendrimers which are shaped like trees with many branches—or tiny tentacles. The number of tentacles exponentially increases with dendrimer size and the tentacles are positioned less than 1 nanometer from each other. The ends of tentacles are where regular patterns appear. Depending on chemical structure of these patterns, they found that these dendrimers could

escape detection by the CPR radar.

Professor Moein Moghimi explains: "This discovery shows that we can develop certain dendrimers as very tiny carriers to smuggle drugs into the body without triggering our immune system. Activation of the complement system as the defense mechanisms of our immune system can sometimes result in inflammation and may also induce anaphylactic reactions. One example is we have seen anaphylaxis in some recipients of COVID-19 vaccines, which uses small lipid particles and instead with dendrimers we could avoid these adverse reactions."

Avoiding triggering our immune system

"Dendrimers offer us the ability to deliver drugs to diseased sites where inflammation is a major problem such as in conditions like atherosclerosis, cancer, macular degeneration and rheumatoid arthritis," said Dr. Panagiotis Trohopoulos, cardiologist and managing director of CosmoPHOS Ltd (Thessaloniki, Greece), co-author of the paper.

"This could allow medical teams to treat these conditions without triggering the patient's own immune system. That is why we chose dendrimers in an ongoing therapeutic study in atherosclerosis," said Dr. Trohopoulos.

The team suggests that since these complement-evading dendrimers are so tiny they could also be used to camouflage surfaces of implants and many biomedical devices like cardiovascular stents, protecting them against attack by the complement system.

The researchers also say that these findings suggest that some very dangerous bacteria and viruses could be exploiting patterns to escape our immune system. For example, it might be possible that pathogens display surface patterns with less than 1 nanometer periodicity from each other

in order to escape the complement system radar and survive inside the host.

Finally, the team also found that a special type of dendrimer (those bearing amine groups on their tentacles) hitchhike on an immune molecule called immunoglobulin M (IgM). "With these dendrimers the ride was not free; jumping on IgM dented its structure and this triggered the complement response," said Prof. Moghimi.

The interdisciplinary team intends to develop the work further examining the potential for drug delivery, vaccine design, and device bioengineering, as well as the basic understanding of microbial evasion from our immune system.

More information: Lin-Ping Wu et al, Dendrimer end-terminal motif-dependent evasion of human complement and complement activation through IgM hitchhiking, *Nature Communications* (2021). DOI: 10.1038/s41467-021-24960-6

Provided by Newcastle University

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