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– Chemical Biology –

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Scope of Research

Chemical biology is an interdisciplinary field of study that is often defined as "chemistry-initiated biology." As biological processes all stem from chemical events, it should be possible to understand or manipulate biological events using chemistry. Our laboratory has been discovering or designing unique organic molecules that modulate fundamental processes in human cells. Such synthetic organic molecules often serve as tools for basic cell biology. Discovery or design of small molecules with unique biological activities permits small-molecule-initiated exploration of complex cellular events. Our mission is to create a new world of bioactive synthetic molecules: new modes of activity, new shapes, and new sizes. We hope that these basic studies open new avenues for small-molecule applications in a range of fields.

KEYWORDS

Chemical Biology Self-Assembly Chemical Library
Chemical Genetics Immunology

Recent Selected Publications

Perron, A.; Mandal, S.; Chuba, T.; Mao, D.; Singh, V.; Noda, N.; Tan, R.; Vu, H.; Abo, M.; Uesugi, M., Small-Molecule Drug Repurposing for Counteracting Phototoxic A2E Aggregation, *ACS Chem. Biol.*, **18(10),** 2170-2175 (2023).

Zhuo, S.; Noda, N.; Hioki, K.; Jin, S.; Hayashi, T.; Hiraga, K.; Momose, H.; Li, W.; Zhao, L.; Mizukami, T.; Ishii, K.; Li, Y.; Uesugi, M., Identification of a Self-Assembling Small-Molecule Cancer Vaccine Adjuvant with an Improved Toxicity Profile, *J. Med. Chem.*, **66(18),** 13266-13279 (2023).

Toh, K.; Nishio, K.; Nakagawa, R.; Egoshi, S.; Abo, M.; Perron, A.; Sato, S.; Okumura, N.; Koizumi, N.; Dodo, K.; Sodeoka, M.; Uesugi, M., Chemoproteomic Identification of Blue-Light-Damaged Proteins, *J. Am. Chem. Soc.*, **144,** 20171-20176 (2022).

Jin, S.; Zhuo, S.; Takemoto, Y.; Li, Y.; Uesugi, M., Self-Assembling Small-Molecule Adjuvants as Antigen Nano-Carriers, *Chem Commun.*, **58,** 12228-12231 (2022).

Nishio, K.; Toh, K.; Perron, A.; Goto, M.; Abo, M.; Shimakawa, Y.; Uesugi, M., Magnetic Control of Cells by Chemical Fabrication of Melanin, *J. Am. Chem. Soc.*, **144,** 16720-16725 (2022).

Small-Molecule Drug Repurposing for Counteracting Phototoxic A2E Aggregation

Despite the well-established role of oxidative stress in the pathogenesis of age-related macular degeneration (AMD), the mechanism underlying phototoxicity remains unclear. The Uesugi group used a drug repurposing approach to isolate an FDA-approved drug that blocks the aggregation of the photoinducible major fluorophore of lipofuscin, the bis-retinoid N-retinylidene-N-retinylethanolamine (A2E). Their fluorescence-based screening combined with dynamic light scattering (DLS) analysis led to the identification of entacapone as a potent inhibitor of A2E fluorescence and aggregation. The entacapone-mediated inhibition of A2E aggregation blocks its photodegradation and offers photoprotection in A2E-loaded retinal pigment epithelial (RPE) cells exposed to blue light. In-depth mechanistic analysis suggests that entacapone prevents the conversion of toxic aggregates by redirecting A2E into off-pathway oligomers. These findings provide evidence that aggregation contributes to the phototoxicity of A2E.

Identification of a Self-Assembling Small-Molecule Cancer Vaccine Adjuvant with an Improved Toxicity Profile

Protein or peptide cancer vaccines usually include immune potentiators, so-called adjuvants. However, it remains challenging to identify structurally simple, chemically accessible synthetic molecules that are effective and safe as vaccine adjuvant. The Uesugi group discovered cholicamideβ (6), a self-assembling small-molecule vaccine adjuvant with an improved toxicity profile and proven efficacy in vivo. The Uesugi group and their collaborators demonstrated that cholicamideβ (6), which is less cytotoxic than its parent compound, forms virus-like particles to potently activate dendritic cells with the concomitant secretion of cytokines. When combined with a peptide antigen, cholicamideβ (6) potentiated the antigen presentation on dendritic cells to induce antigen-specific T cells. As a therapeutic cancer vaccine adjuvant in mice, a mixture of cholicamideβ (6) and a peptide antigen protected mice from the challenges of malignant cancer cells without overt toxicity. Cholicamideβ (6) may offer a translational opportunity as an unprecedented class of small-molecule cancer vaccine adjuvants.