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A CHIMIA Column

Short Abstracts of Interesting Recent Publications of Swiss Origin

Site-specific Modification of Native IgGs with Flexible Drug-Load

Jöri E. Wehrmüller, Julia C. Frei, Torsten Hechler, Michael Kulke, Andreas Pahl, Martin Béhé, Roger Schibli*, and Philipp R. Spycher*

ChemBioChem **2024**, e202400511
https://doi.org/10.1002/cbic.202400511

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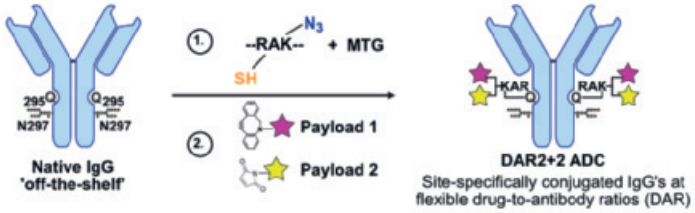
Antibody-drug conjugates (ADCs) offer precise drug delivery to target tissues, but their development faces challenges like drug-to-antibody ratio (DAR) heterogeneity and the need for complex engineering. A novel method has been introduced that leverages microbial transglutaminase (MTG) to site-specifically modify native IgGs at glutamine 295 (Q295) using short, positively charged lysine-containing peptides. This technique eliminates the need for antibody engineering or glycosylation removal, ensuring antibody stability and full biological activity. Proof-of-concept studies with trastuzumab, a HER-2-targeting antibody, demonstrated the flexibility to generate ADCs with defined DARs (2 and 4) and dual payloads. *In vitro* and *in vivo* tests showed high stability, specific tumor accumulation, and potent efficacy. Notably, an ADC armed with the cytotoxic compound α-Amanitin achieved complete and sustained tumor remission in a HER-2 positive xenograft model. This simple, versatile approach paves the way for efficient production of homogeneous, stable ADCs for therapeutic and diagnostic applications.

Authors' comments:
"We demonstrate a straightforward method for generating precise antibody conjugates directly from native antibodies using MTG, bypassing N297 glycosylation removal, by employing short, positively charged lysine-containing peptides for site-specific modification at Q295."



Anion Exchange Membrane Water Electrolysis at 10 A·cm^{-2} Over 800 Hours

Yiwei Zheng, Wenchao Ma, Ariana Serban, Andrit Allushi, and Xile Hu*

Angew. Chem. Int. Ed. **2024**, e202413698
https://doi.org/10.1002/anie.202413698

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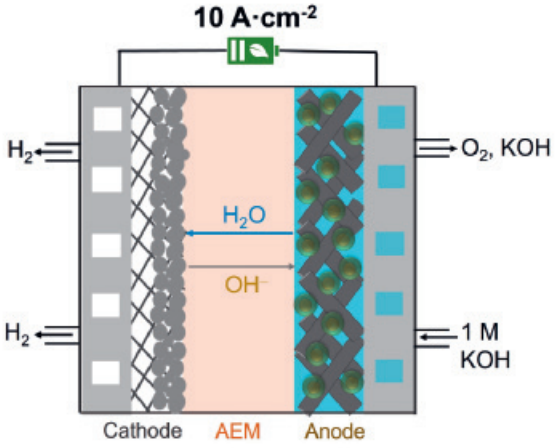
Anion exchange membrane water electrolyzers (AEMWEs) are a promising, low-cost solution for producing green hydrogen. Standard AEMWEs typically operate at current densities below 3 A·cm^{-2}. Higher current densities have the potential to significantly reduce hydrogen production costs, but are largely unexplored. In this study, we tackle this problem by optimizing AEMWE components such as a more conductive and durable membrane, tailored ionomers, advanced catalysts, and an improved porous transport layer. These enhancements enable stable operation at an ultrahigh current density of 10 A·cm^{-2}, with lifetimes over 800 hours – a five-order-of-magnitude improvement over existing benchmarks. The cell voltage of 2.3 V at 10 A·cm^{-2} is comparable to the most advanced AEMWE devices operating at much lower densities. This highlights the potential of ultrahigh-density AEMWEs in advancing cost-efficient hydrogen production.

Authors' comments:
"Our work aims to bring greater attention to the high-current-density operation mode of Anion Exchange Membrane Water Electrolyzers (AEMWE), a topic that has received limited focus despite its economic potential. We successfully identified strategies for achieving highly durable AEMWE performance at ultra-high current densities."



Prepared by Cesare Berton, James Southwell, Jonas Genz, Stanislav Prytuliak, Fan Liu, Eda Nisli, Deborah Bäcker, Perle Hermant, Samy Kichou, Ben Boback, Dominik Ernst, Tiago Rosa de Araujo, Ian Saxer, Liam Wenger, Henrik Braband, and Jason P. Holland*
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Total Synthesis of (–)-Bipolarolide D

Gleb A. Chesnokov, Julia Friedli, Francis J. Carta, and Karl Gademann*

JACS Au, **2024**, *4*, 4194
https://doi.org/10.1021/jacsau.4c00680

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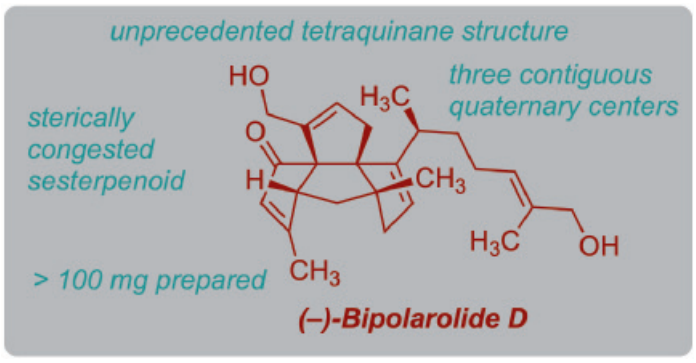
The synthesis of structurally complex terpenoids like (–)-bipolarolide D is challenging due to their intricate architecture. Here, an efficient approach to the (–)-bipolarolide D total synthesis is demonstrated, achieving a 1.8% overall yield through a series of optimized steps. The process features a Pauson-Khand reaction to establish the core diquinane structure, a Rautenstrauch cycloisomerization to install a cyclopentenone, and a radical cyclization to construct the tetraquinane scaffold. Additional transformations include a crotylation with 1-methyl-2-propenylmagnesium chloride to attach the side chain. Finally, a Suzuki coupling produced (–)-bipolarolide D. This strategy yields over 100 mg of product. Compared to another recent approach, this route quadrupled the yield and enhanced scalability, making it a promising method for synthesizing structurally complex sesterpenoids.

Authors' comments:

"The highly complex architecture inspired us to tackle this challenge. We are really happy that we could develop such a scalable route, delivering significant amounts of the synthetic natural product."



DNA-Based Chemical Unclonable Functions for Cryptographic Anticounterfeit Tagging of Pharmaceuticals

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ACS Nano, **2024**, *18*, 30774
https://doi.org/10.1021/acsnano.4c10870

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The paper introduces DNA-based Chemical Unclonable Functions (CUFs) for combating counterfeit pharmaceuticals. These CUFs use random DNA oligos encapsulated *in silica* for integration directly into products like acetaminophen. The system leverages cryptographic authentication through unique, unclonable DNA pools that remain stable for years. A simplified workflow using Sanger sequencing ensures accurate and cost-effective authentication. Experimental results confirm the method's durability, reliability, and security against replication. This innovation extends beyond pharmaceuticals, offering scalable, secure, and versatile anticounterfeit tagging across diverse industries.

Authors' comments:

"We are fascinated by random DNA synthesis as a manifestation of molecular chaos and entropy. Here we show how it can be brought to practical use through the power of PCR and sequencing."