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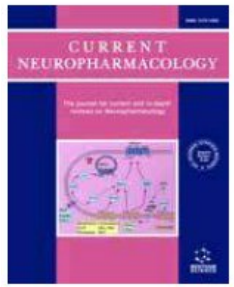

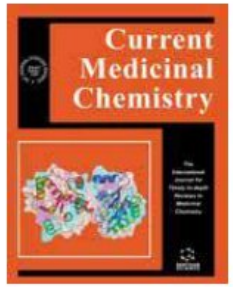

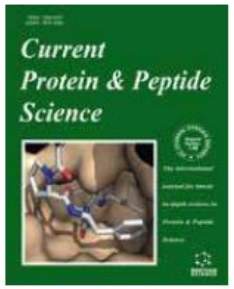

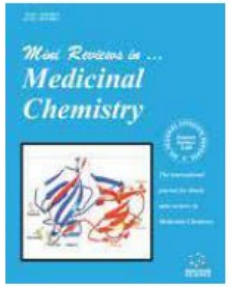

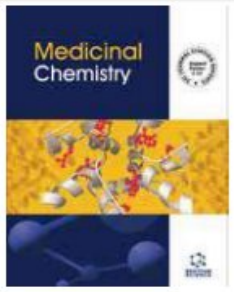

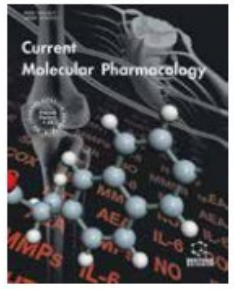

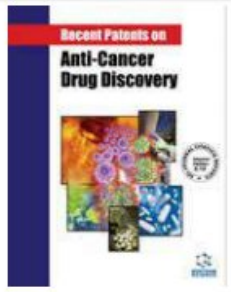

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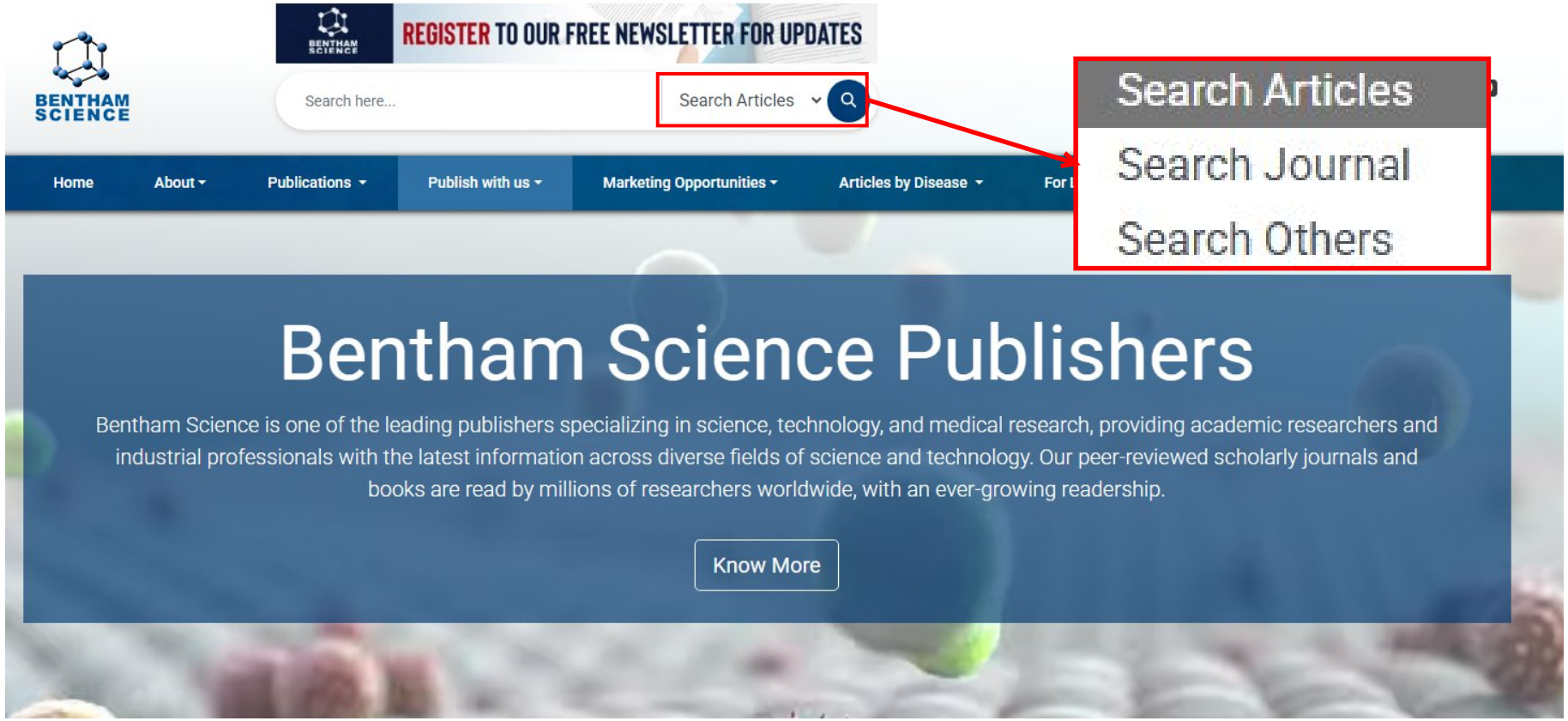

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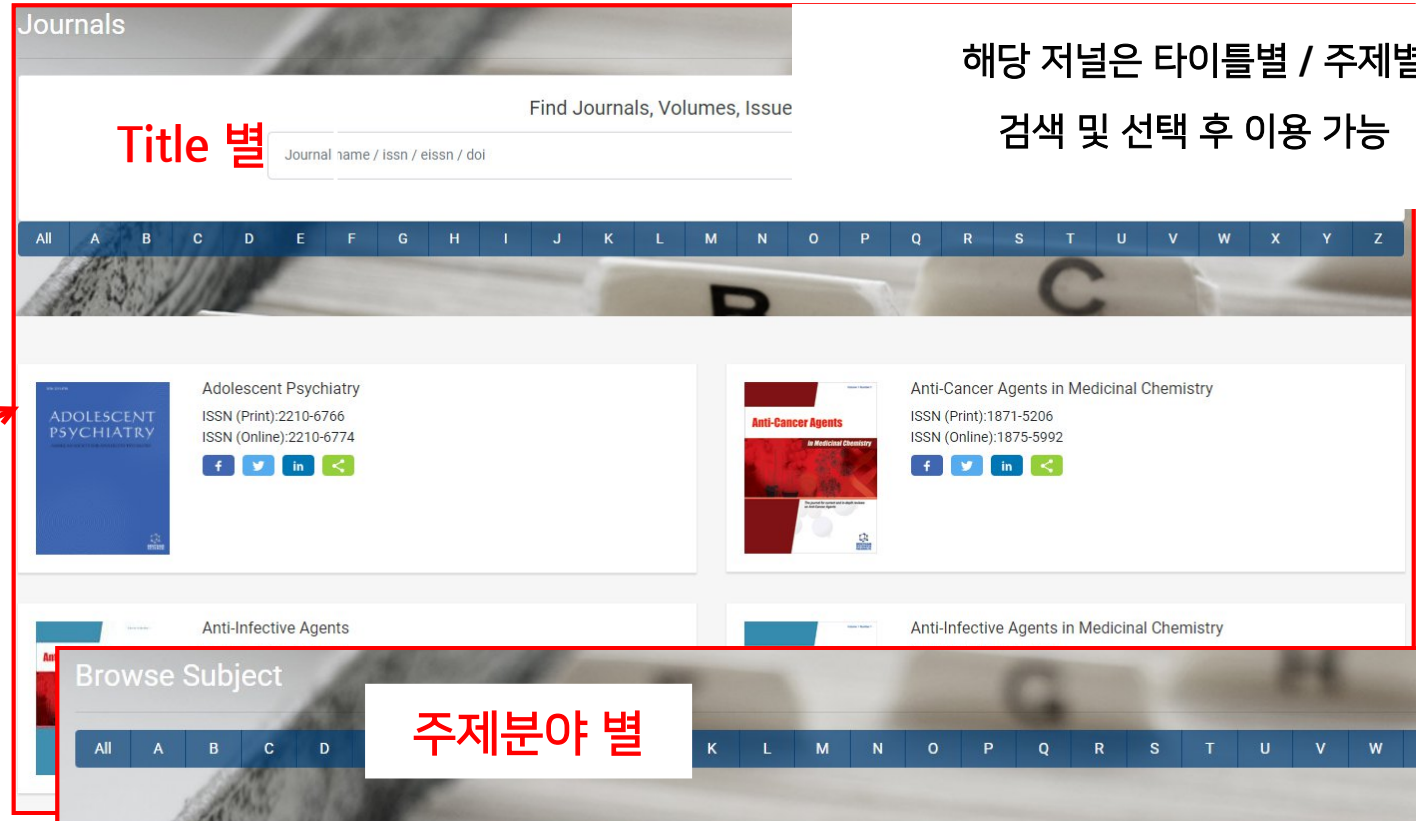

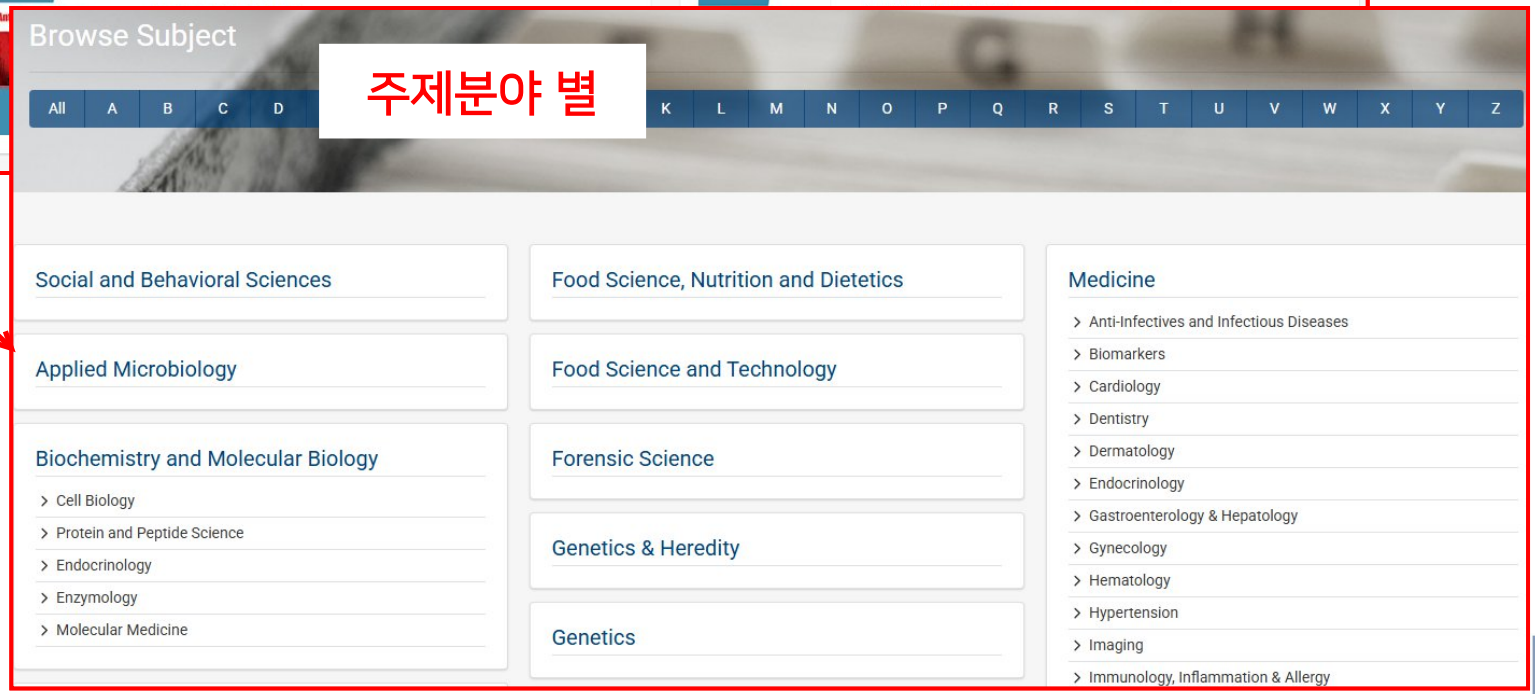

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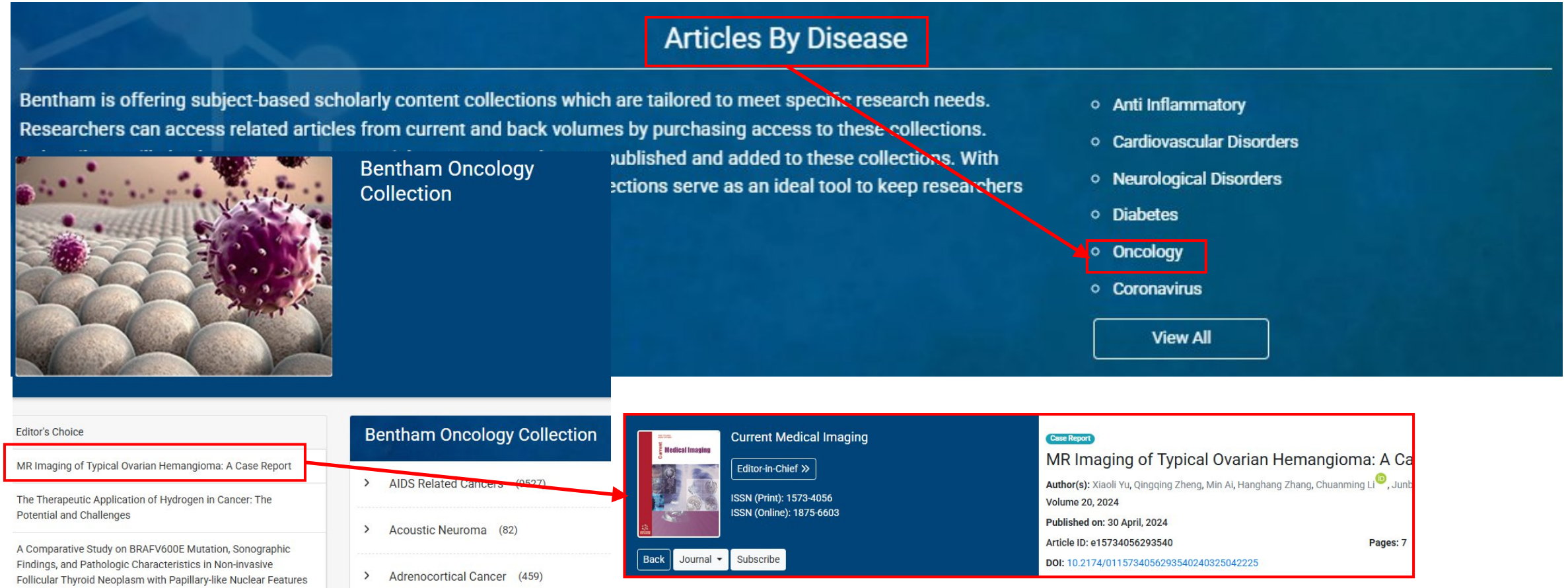

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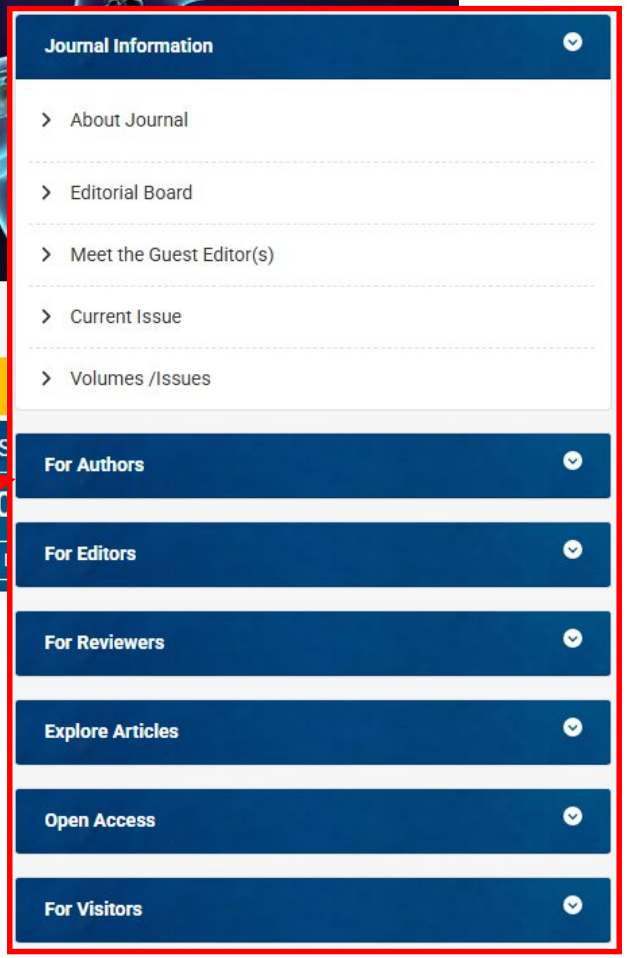

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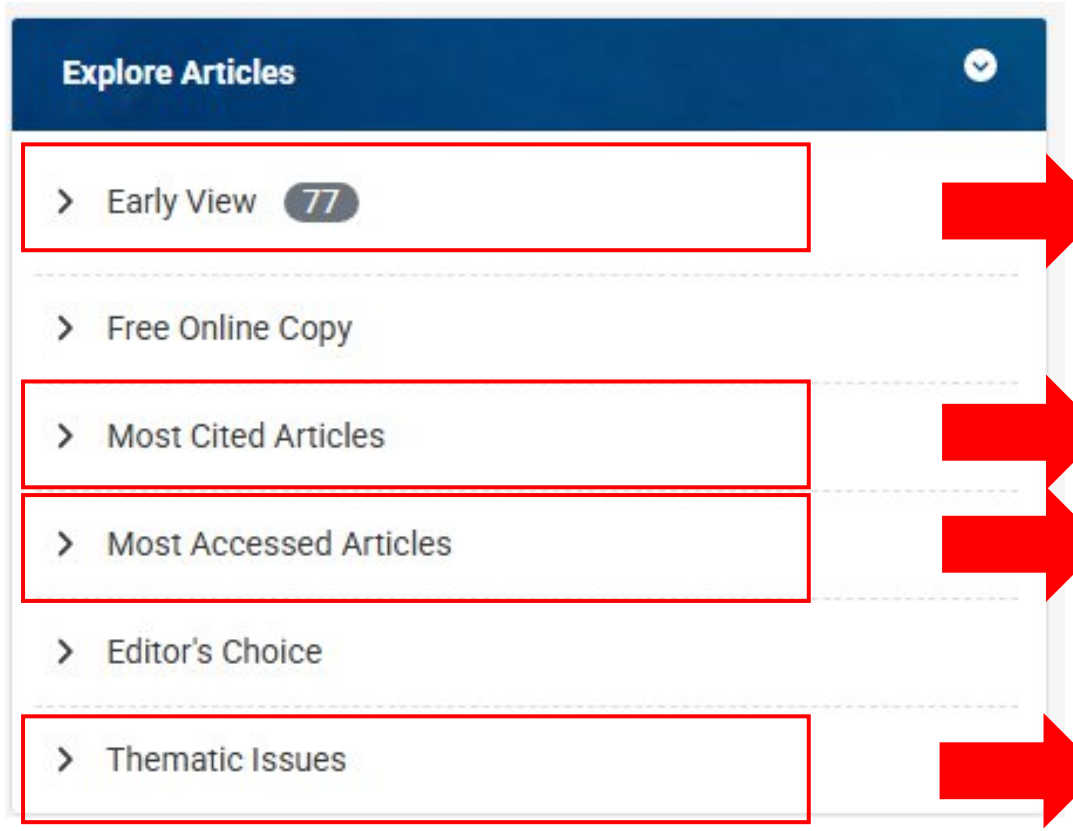

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Review Article

Pharmacodynamics and Pharmacokinetics of Ublituxim
Multiple Sclerosis Treatment

In Press. Available online August 27, 2025

Authors: Monica Margoni, Luca Battistini, Diego Centonze, Roberto Furla

DOI: 10.2174/011570159X392955250815095236

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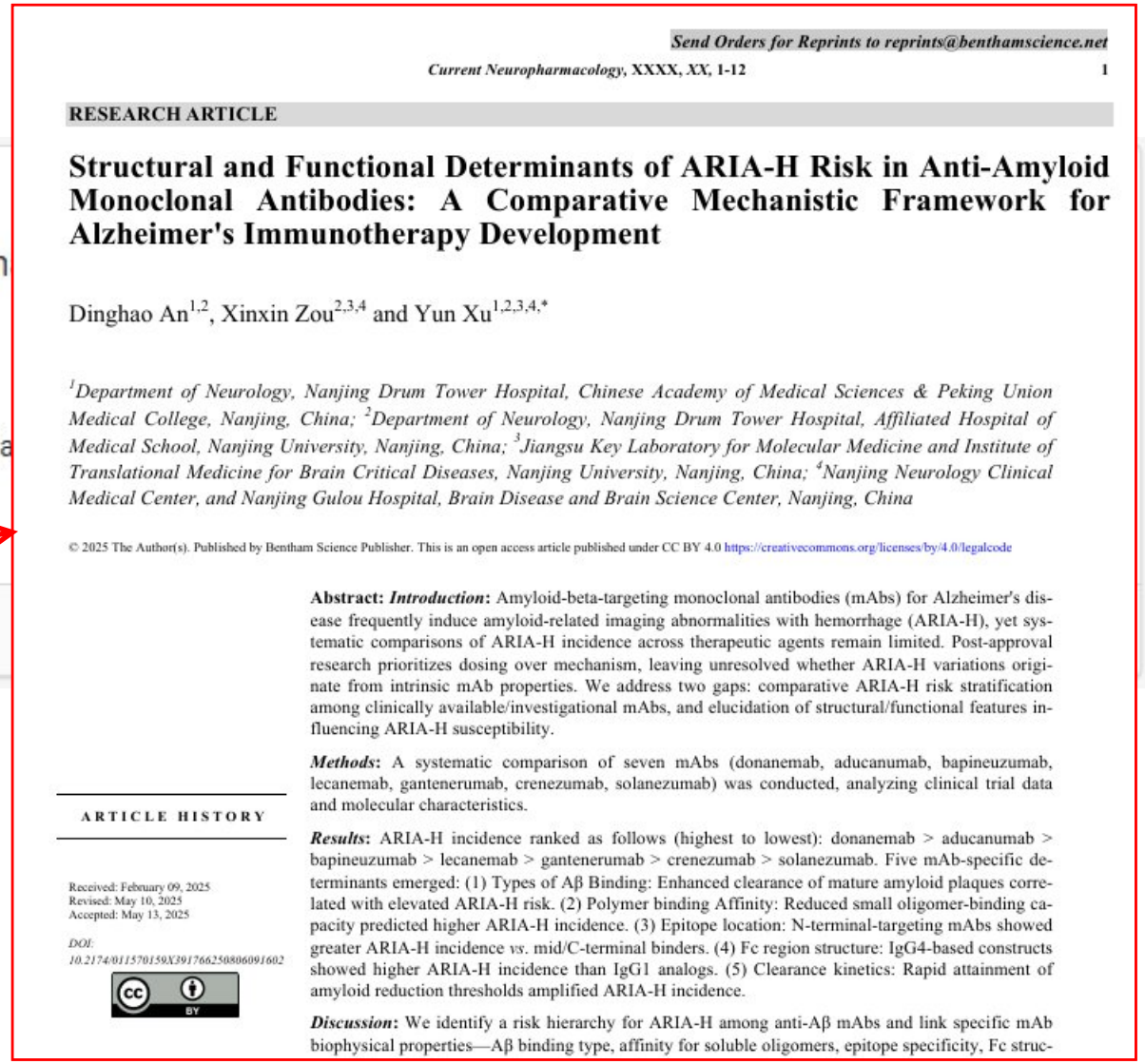

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Current Neuropharmacology, XXXX, XX, 1-12 1

RESEARCH ARTICLE

Structural and Functional Determinants of ARIA-H Risk in Anti-Amyloid Monoclonal Antibodies: A Comparative Mechanistic Framework for Alzheimer's Immunotherapy Development

Dinghao An[1,2], Xinxin Zou[2,3,4] and Yun Xu[1,2,3,4,*]

[1]Department of Neurology, Nanjing Drum Tower Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Nanjing, China; [2]Department of Neurology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China; [3]Jiangsu Key Laboratory for Molecular Medicine and Institute of Translational Medicine for Brain Critical Diseases, Nanjing University, Nanjing, China; [4]Nanjing Neurology Clinical Medical Center, and Nanjing Gulou Hospital, Brain Disease and Brain Science Center, Nanjing, China

Abstract: ***Introduction*:** Amyloid-beta-targeting monoclonal antibodies (mAbs) for Alzheimer's disease frequently induce amyloid-related imaging abnormalities with hemorrhage (ARIA-H), yet systematic comparisons of ARIA-H incidence across therapeutic agents remain limited. Post-approval research prioritizes dosing over mechanism, leaving unresolved whether ARIA-H variations originate from intrinsic mAb properties. We address two gaps: comparative ARIA-H risk stratification among clinically available/investigational mAbs, and elucidation of structural/functional features influencing ARIA-H susceptibility.

***Methods*:** A systematic comparison of seven mAbs (donanemab, aducanumab, bapineuzumab, lecanemab, gantenerumab, crenezumab, solanezumab) was conducted, analyzing clinical trial data and molecular characteristics.

***Results*:** ARIA-H incidence ranked as follows (highest to lowest): donanemab > aducanumab > bapineuzumab > lecanemab > gantenerumab > crenezumab > solanezumab. Five mAb-specific determinants emerged: (1) Types of Aβ Binding: Enhanced clearance of mature amyloid plaques correlated with elevated ARIA-H risk. (2) Polymer binding Affinity: Reduced small oligomer-binding capacity predicted higher ARIA-H incidence. (3) Epitope location: N-terminal-targeting mAbs showed greater ARIA-H incidence *vs.* mid/C-terminal binders. (4) Fc region structure: IgG4-based constructs showed higher ARIA-H incidence than IgG1 analogs. (5) Clearance kinetics: Rapid attainment of amyloid reduction thresholds amplified ARIA-H incidence.

***Discussion*:** We identify a risk hierarchy for ARIA-H among anti-Aβ mAbs and link specific mAb biophysical properties—Aβ binding type, affinity for soluble oligomers, epitope specificity, Fc struc-

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