GetFTR: Providing Pathways to Trusted Research

Ralph Youngen

Senior Director, Digital Partnerships at ACS

Chair of the Board, Get Full Text Research (GetFTR)

GET FULLTEXT RESEARCH

GET FULLTEXT RESEARCH

The GetFTR service was launched in 2020 with support from leading scholarly publishers:

ACS Publications

SPRINGER NATURE

ELSEVIER

Taylor & Francis Group
an informa business

WILEY

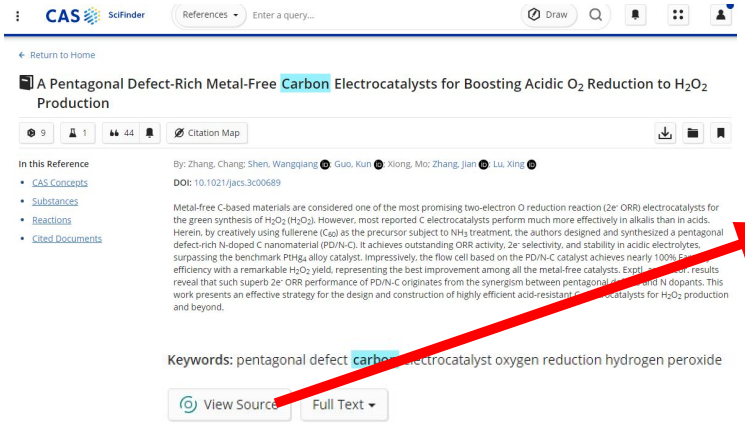
GETFTR
getfulltextresearch.com

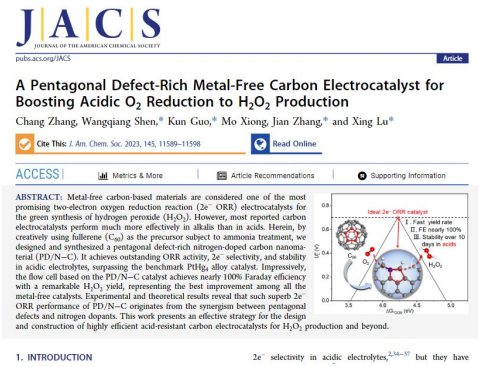
GetFTR works with publishers and discovery resources to ensure researchers can easily discover and access the content they are entitled to read.

GetFTR simplifies the pathway from research discovery tools to full-text content.

For example:

CAS SciFinder → GET FULLTEXT RESEARCH → JACS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY





GetFTR has widespread support across publishers, with more than 66% of full-text research content supported.

PUBLISHERS

- AAAS
- AACR
- ACS
- ADA
- AIP Publishing
- AIAA
- AMA
- APA
- AMS
- APS
- ASCE
- ASM
- ASM International
- CABI
- Dovepress
- Edinburgh University Press
- Edward Elgar
- Elsevier
- Future Science Group
- Geological Society of London
- IOP Publishing
- Karger
- Oxford University Press
- Rockefeller University Press
- Royal College of Surgeons of London
- Sage
- Springer Nature
- Taylor & Francis
- Thieme
- Wageningen Academic Publishers
- Wiley

GetFTR also has widespread support across research discovery systems.

DISCOVERY TOOLS

- APA Psychinfo
- Cactus
- CHORUS
- DeepDyve
- Digital Science
- Dimensions
- Figshare
- Mendeley
- MyScienceWork
- Readcube Papers
- Researcher
- ResearchGate
- SciFinder
- SciSummary
- Scopus
- Semantic Scholar
- SN Experiments
- Symplectic

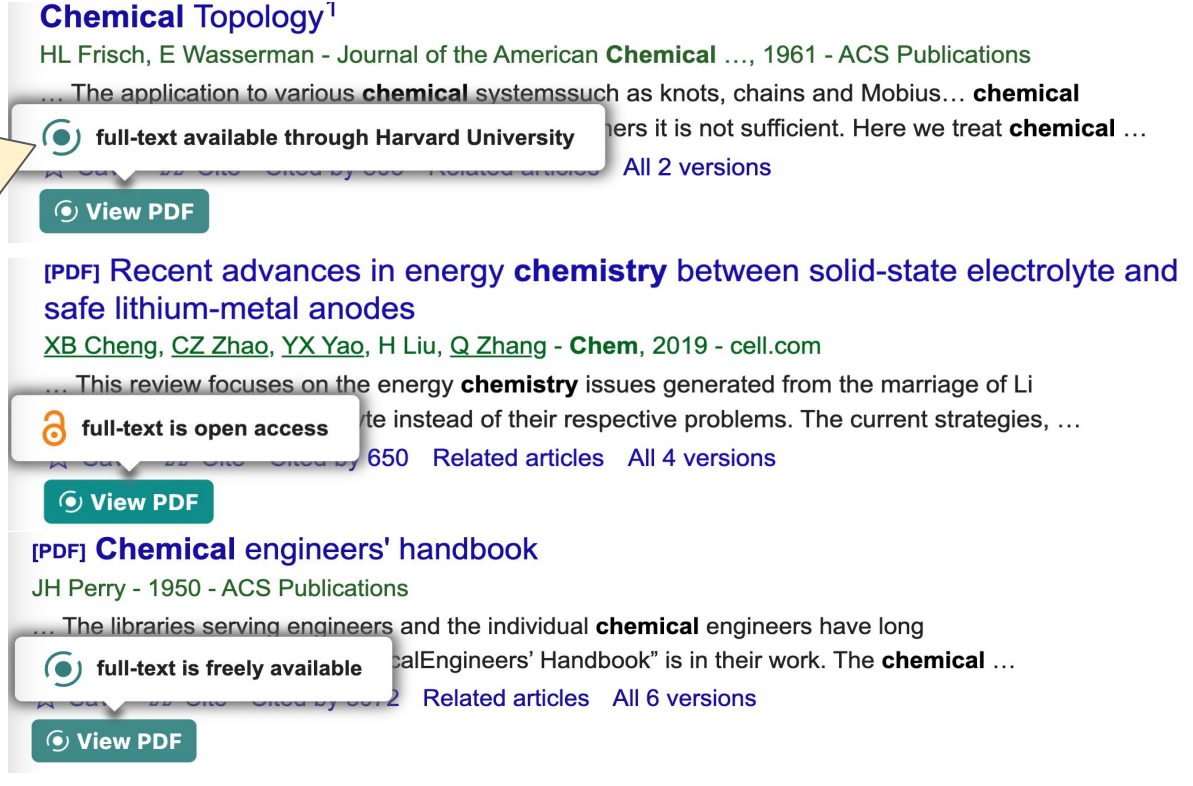
THE FREE BROWSER EXTENSION* SUPPORTS ADDITIONAL DISCOVERY TOOLS

- Google Scholar
- Google
- PubMed
- Proquest Summons
- EBSCO
- Primo
- Web of Science
- Microsoft Bing
- Lens
- DOIs on any site

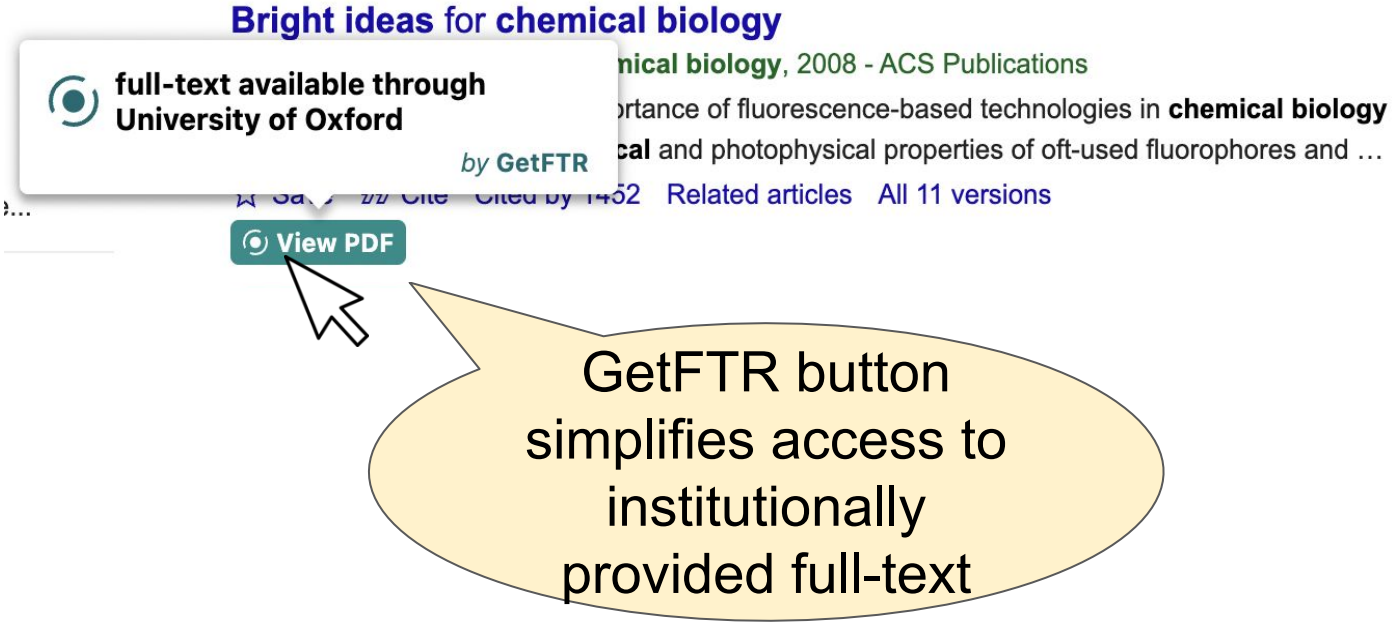
*Chrome, Firefox, Edge

GetFTR Button Signals Full-Text Availability

GetFTR signals full text availability via an institutional subscription, Open Access, or freely available.



Researchers may seek alternate versions even when their institution has subscribed to the article



Researchers spend a lot of time navigating publisher websites to authenticate and access content

ACS chemical biology

Letters

pubs.acs.org/acschemicalbiology

Selective Small Molecule Induced Degradation of the BET Bromodomain Protein BRD4

Michael Zengerle, Kwok-Ho Chan, and Alessio Ciulli*

College of Life Sciences, Division of Biological Chemistry and Drug Discovery, University of Dundee, James Black Centre, Dow Street, Dundee, DD1 5EH, United Kingdom

Supporting Information

ABSTRACT: The Bromo- and Extra-Terminal (BET) proteins BRD2, BRD3, and BRD4 play important roles in transcriptional regulation, epigenetics, and cancer and are the targets of pan-BET selective bromodomain inhibitor JQ1. However, the lack of intra-BET selectivity limits the scope of current inhibitors as probes for target validation and could lead to unwanted side effects or toxicity in a therapeutic setting. We designed Proteolysis Targeted Chimeras (PROTACs) that tether JQ1 to a ligand for the E3 ubiquitin ligase VHL, aimed at triggering the intracellular destruction of BET proteins. Compound MZ1 potently and rapidly induces reversible, long-lasting, and unexpectedly selective removal of BRD4 over BRD2 and BRD3. The activity of MZ1 is dependent on binding to VHL but is achieved at a sufficiently low concentration not to induce stabilization of HIF-1α. Gene expression profiles of selected cancer-related genes responsive to JQ1 reveal distinct and more limited transcriptional responses induced by MZ1, consistent with selective suppression of BRD4. Our discovery opens up new opportunities to elucidate the cellular phenotypes and therapeutic implications associated with selective targeting of BRD4.

The Bromo- and Extra-terminal (BET) family of proteins, including the ubiquitously expressed BRD2, BRD3, and BRD4 and the testis-specific BRDT, recruit transcriptional regulatory complexes to acetylated chromatin thereby controlling specific networks of genes involved in cellular proliferation and cell cycle progression.[1] Deregulation of BET protein activity, in particular BRD4, has been strongly linked to cancer and inflammatory diseases, making BET proteins attractive drug targets.[2] For example, RNAi screens have identified BRD4 as a therapeutic target in acute myeloid leukemia,[3] ovarian carcinoma,[4] and siRNA knock down of BRD4, but not of BRD2 or BRD3, induced upregulation of apolipoprotein A1 (ApoA1), which protects from atherosclerosis progression and other inflammatory processes.[5] The silencing of BRD4 furthermore identified BRD4 as a target to treat chronic obstructive pulmonary disease (COPD).[6] These results underscore the potential of targeting BRD4 as a therapeutic strategy and motivate further research in validating BRD4 as a drug target.

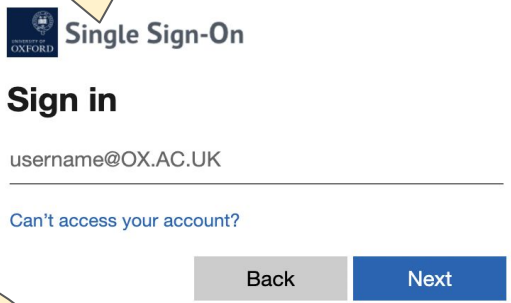
Crucial to the function of BET proteins are two highly homologous bromodomains that are present in their amino-terminal regions and direct recruitment to nucleosomes by binding to specific acetylated lysines (K_{Ac}) within histone tails.[7] Small molecule BET inhibitors, including the triazolodiazepine-based JQ1[8] and I-BET762[9] (Figure 1a) among others,[10−13] bind to the K_{Ac}-binding pocket of the bromodomains and disrupt interaction with histones, thereby displacing BET proteins and their associated transcriptional regulatory complexes from chromatin. BET inhibitors are highly potent (K_d ~100 nM), cell-penetrant, and active *in vivo* against a range of solid, hematological, and other tumors, which has prompted compounds entering phase I clinical trials for cancer.[14−16] However, BET inhibitors show no selectivity for individual BET family members, thereby limiting their scope as chemical probes for validating the roles of individual BET targets in physiology and disease. To this end, chemical genetic strategies have been recently developed to engineer orthogonal sel… BET bromodomain-ligand pairs.[17] While this approach has … advantage of enabling disruption at will of a single or more … bromodomains, it requires a mutation to be introduced into the … target protein. Therapeutically, the effects of BET inhibitors on … different transcriptional pathways have raised concerns about … the safety and tolerability of BET inhibitors in humans. … Crucially, none of the inhibitors described to date is sel… for binding BRD4 bromodomains over those of it… BRD2 and BRD3.

Small molecule chemical probes or inhibitor… post-translational level hold several advant… validation over genetic techniques such as de… mutants or knockouts and RNAi knockdo… affording spatial and temporal control in a rever… A general limitation associated with conventional … driven target inhibition is that it often demands full… engagement, requiring sustained high concentration of a poten…

Received: March 25, 2015
Accepted: June 2, 2015
Published: June 2, 2015

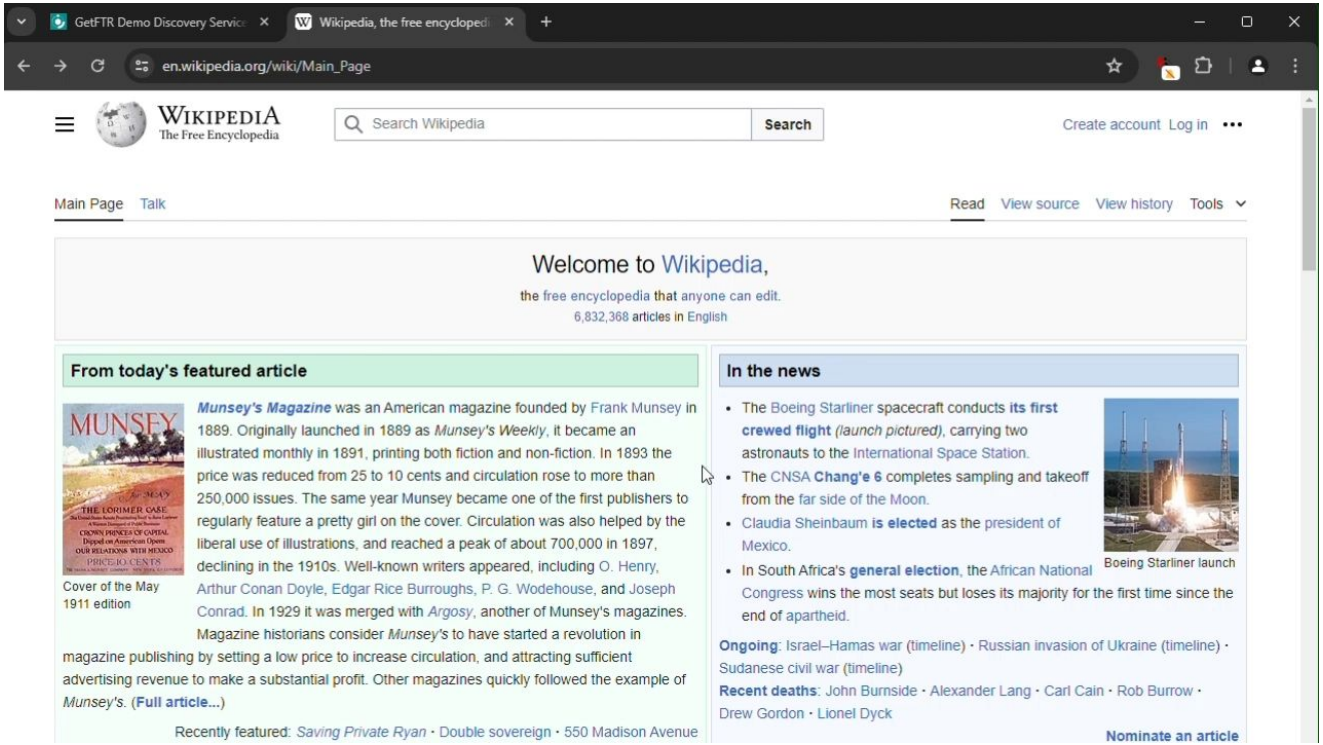
DOI: 10.1021/acschembio.5b00216
ACS Chem. Biol. 2015, 10, 1770−1777

or via institution log in where necessary



GetFTR smart-links provide one-click access to full text

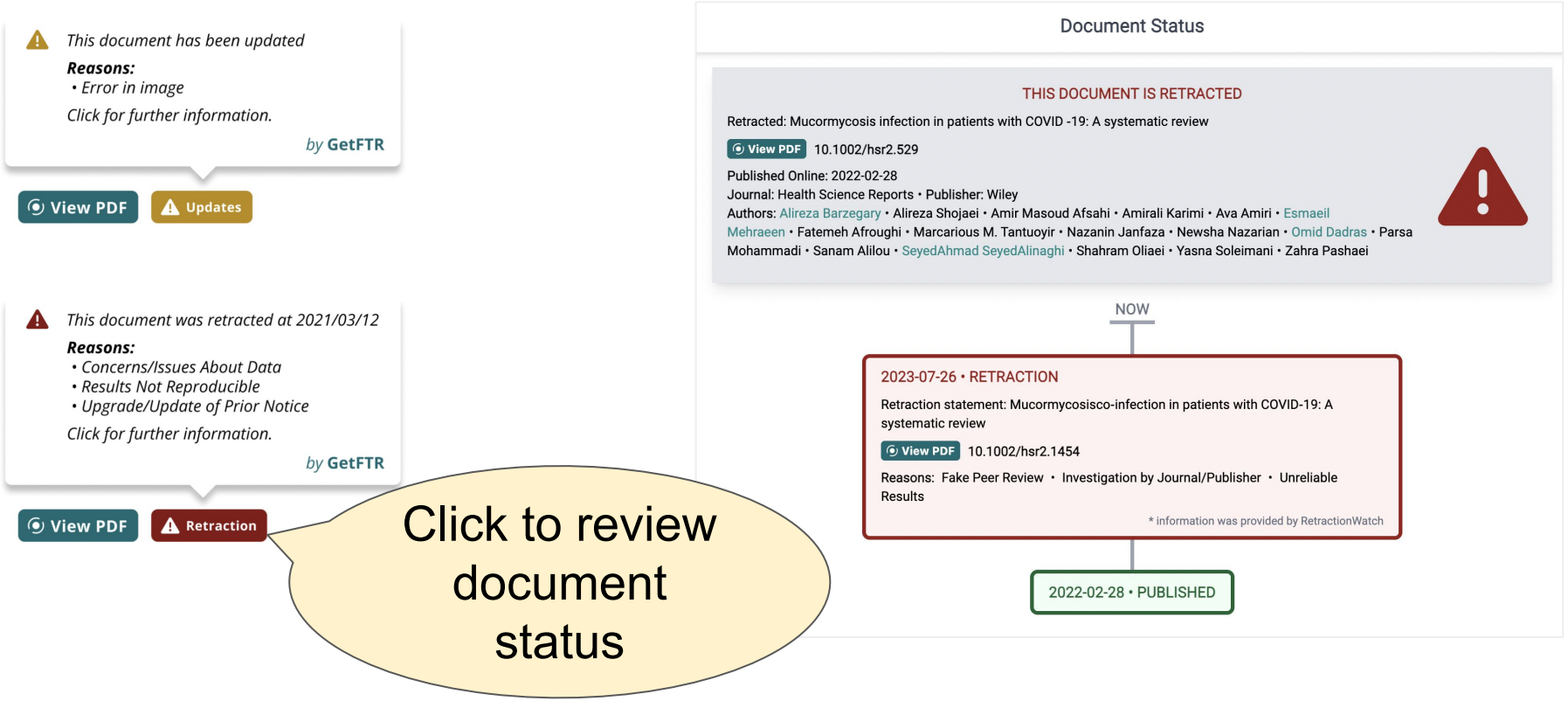
The GetFTR Browser Extension now adds GetFTR links to DOIs on all websites: Here's Wikipedia



GETFTR
getfulltextresearch.com

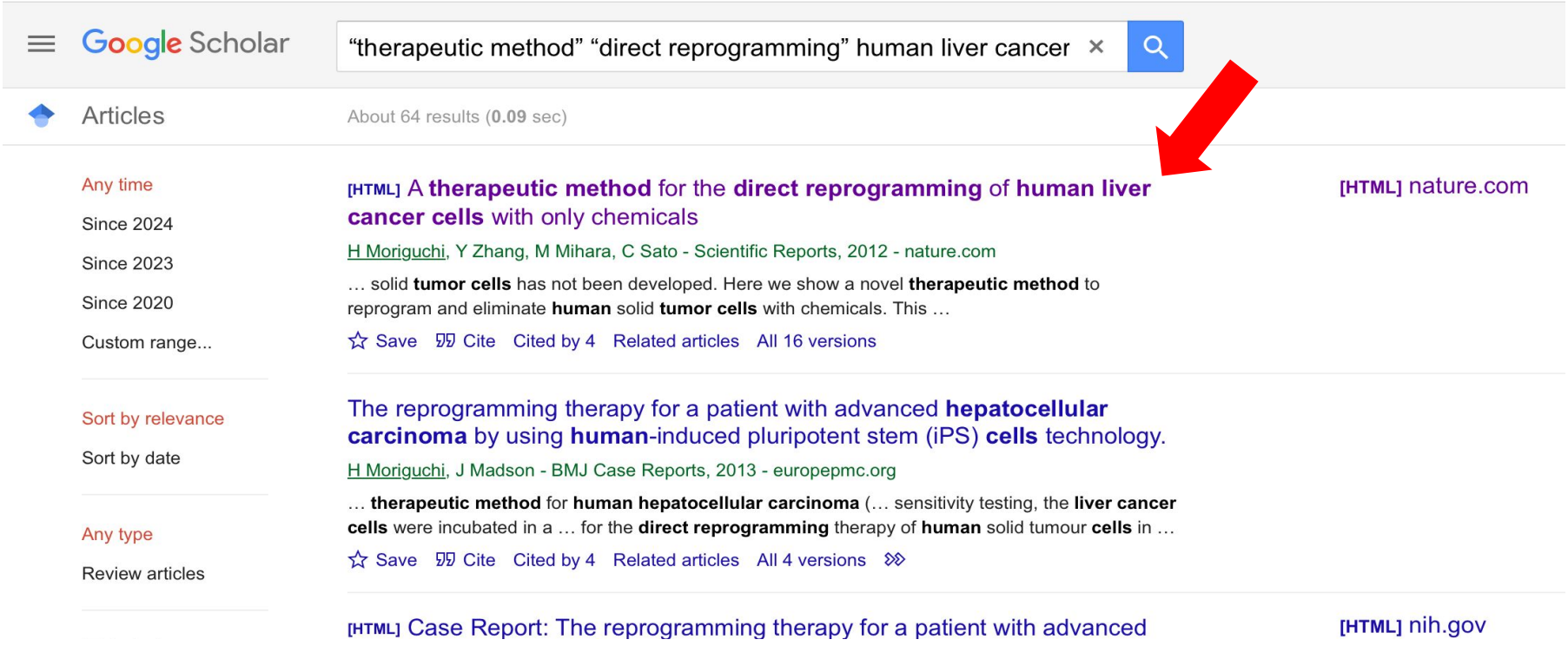
How does GetFTR improve research integrity?

The GetFTR Browser Extension also signals when a document has been updated or retracted



Without the GetFTR Browser Extension

Retractions may not be obvious:



Without the GetFTR Browser Extension

Retractions may not be obvious:

Article | Open access | Published: 21 February 2012

A therapeutic method for the direct reprogramming of human liver cancer cells with only chemicals

Hisashi Moriguchi, Yue Zhang, Makoto Mihara & Chifumi Sato

Scientific Reports **2**, Article number: 280 (2012) | Cite this article

2609 Accesses | **5** Citations | **74** Altmetric | Metrics

A Retraction to this article was published on 09 November 2012

An Addendum to this article was published on 18 October 2012

This article has been updated

Abstract

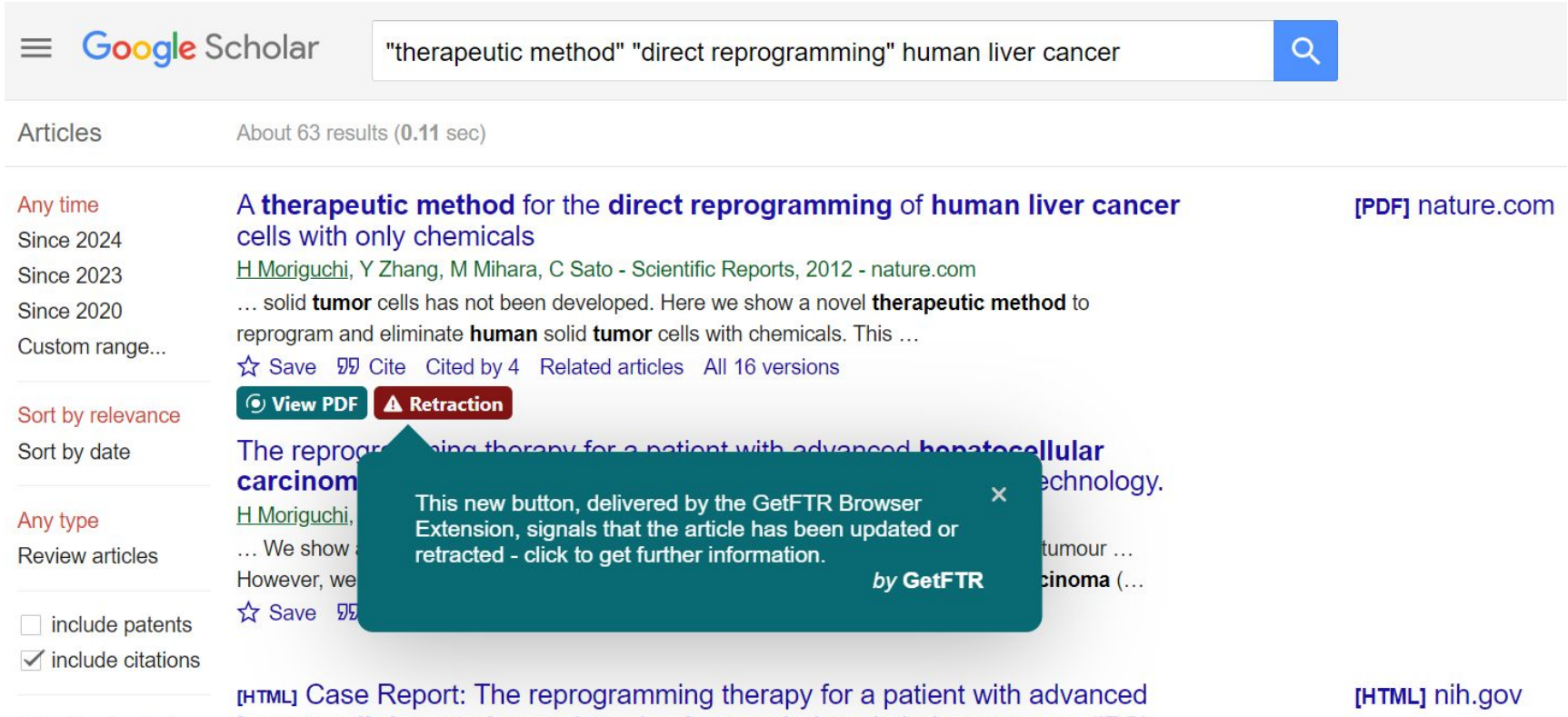
Various methods for the direct reprogramming of human somatic cells have been developed.

Download PDF

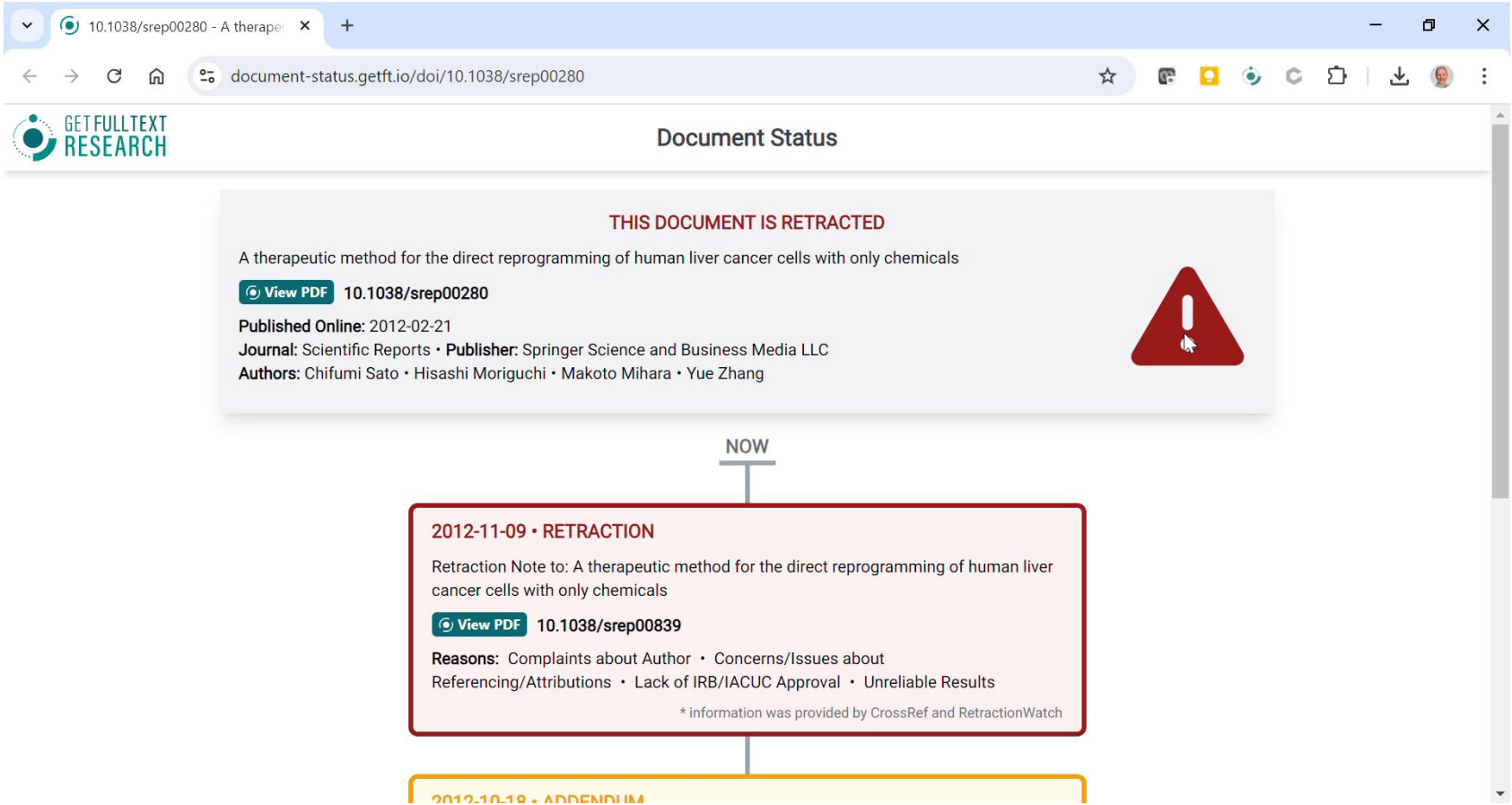
Sections | Figures | References

With the GetFTR Browser Extension

Retraction notices are obvious:



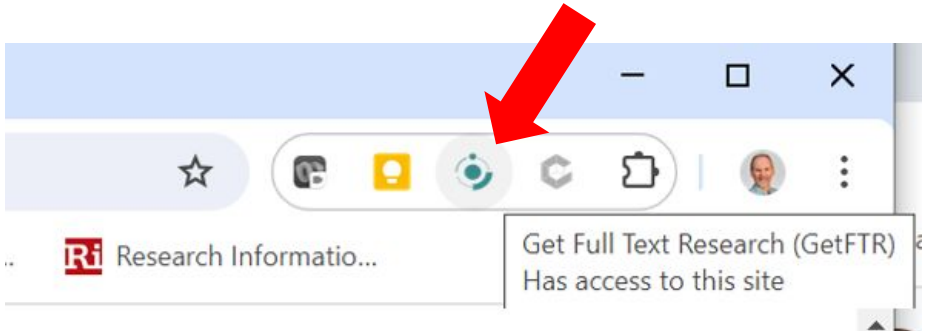
Retraction Notice and Publication History are Provided



GetFTR Browser Extension

Download the GetFTR browser extension

- Chrome Store
- Firefox Store
- Edge



Free GetFTR Browser Extension

https://www.getfulltextresearch.com

Contact Us

joinus@getfulltextresearch.com

GetFTR: Providing Pathways to Trusted Research