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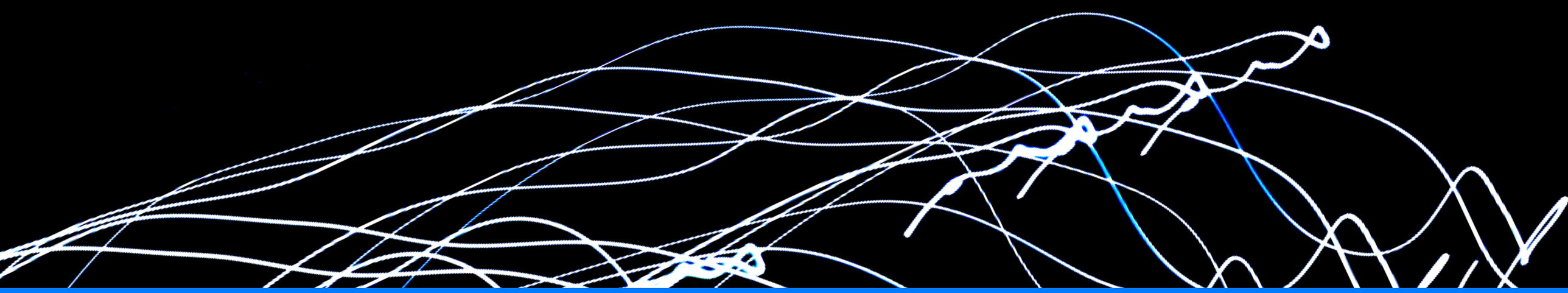

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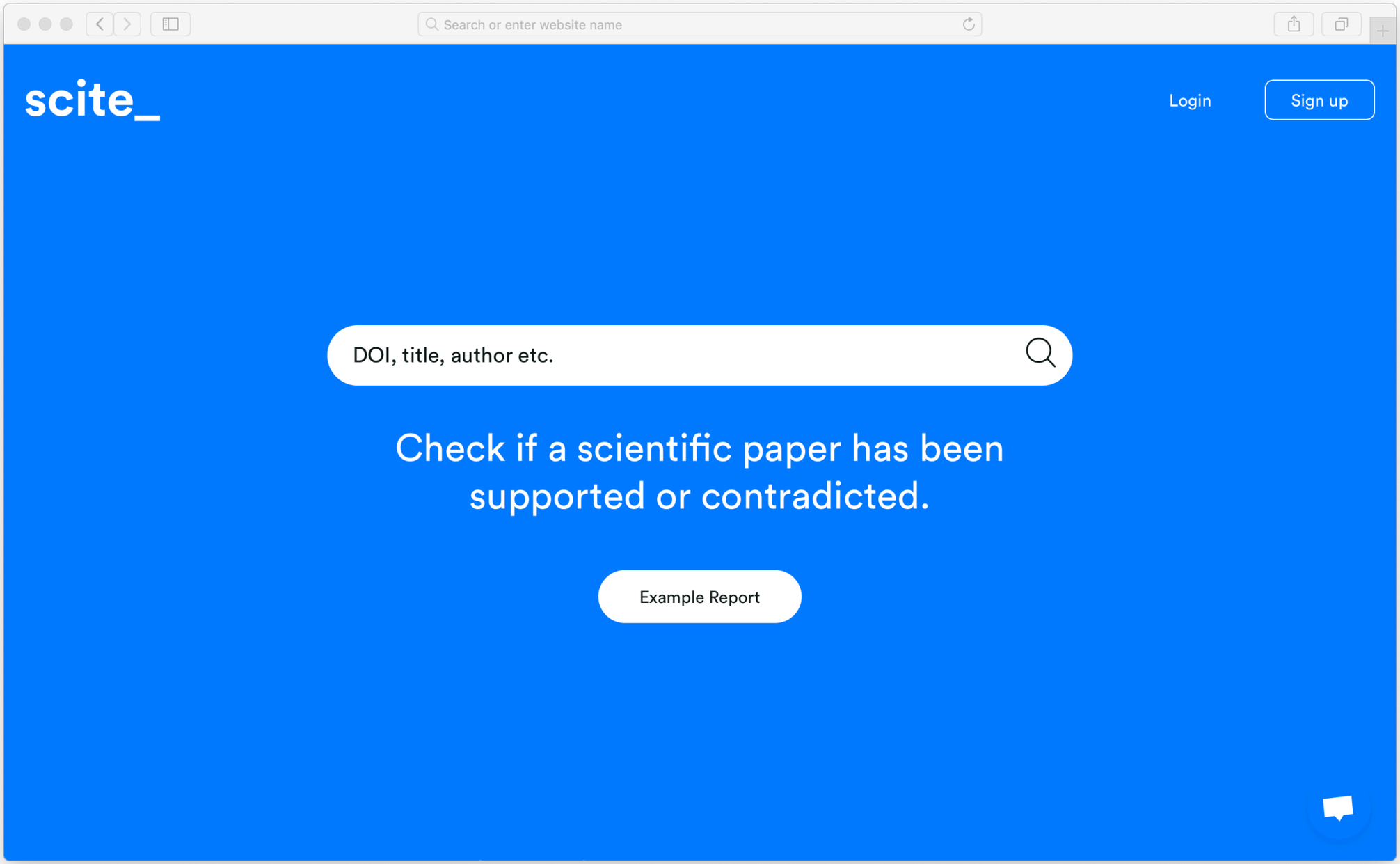
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CELL BIOLOGY, CHROMOSOMES AND GENE EXPRESSION

Chromosome mis-segregation and cytokinesis failure in trisomic human cells

Joshua M Nicholson, Joana C Macedo, Aaron J Mattingly, Darawalee Wangsa, Jordi Camps, Vera Lima, Ana M Gomes, Sofia Dória, Thomas Ried

see all »

Virginia Tech, United States; Universidade do Porto, Portugal; National Institutes of Health, United States

RESEARCH ARTICLE May 5, 2015

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CITE AS: eLife 2015;4:e05068 DOI: 10.7554/eLife.05068

Abstract

Cancer cells display aneuploid karyotypes and typically mis-segregate chromosomes at high rates, a phenotype referred to as *c*hromosomal *in*stability (CIN). To test the effects of aneuploidy on chromosome segregation and other mitotic phenotypes we used the colorectal cancer cell line DLD1 (2n = 46) and two variants with trisomy 7 or 13 (DLD1+7 and DLD1+13), as well as euploid and trisomy 13 amniocytes (AF and AF+13). We found that trisomic cells displayed

eLife DOI: 10.7554/elife.05068

Chromosome mis-segregation and cytokinesis failure in trisomic human cells

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eLife DOI: 10.7554/elife.05068

Chromosome mis-segregation and cytokinesis fa

1 supporting

Supporting 0.81
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Quantitative proteomic and phosphoproteomic comparison of human colon cancer DLD-1 cells differing in ploidy and chromosome stability

Viganó et al. 2018

MBoC Section: Results

Full Text

"...Compared to the diploid parental line, the frequencies of chromosome missegregation and micronuclei formation were significantly elevated in most PTA clones (Figure 2A) but not in the tetraploid line (Figure 2A). In agreement with previous work (***Nicholson et al , 2015***), the trisomic clones showed similar aberrations, albeit to a lesser extent (Supplemental Figure S2B). Furthermore, we observed an increase of structural aberrations in PTA lines and, consistent with earlier work (*Kuznetsova et al , 2015*; *Passerini et al , 2016*), also in trisomic clones (Figure 2B)...."

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Year Published

Letter | Published: 03 August 2011

RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia

Johannes Zuber, Junwei Shi, Eric Wang, Amy R. Rappaport, Harald Herrmann, Edward A. Sison, Daniel Magoon, Jun Qi, Katharina Blatt, Mark Wunderlich, Meredith J. Taylor, Christopher Johns, Agustin Chicas, James C. Mulloy, Scott C. Kogan, Patrick Brown, Peter Valent, James E. Bradner, Scott W. Lowe & Christopher R. Vakoc

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Abstract

Epigenetic pathways can regulate gene expression by controlling and interpreting chromatin modifications. Cancer cells are characterized by altered epigenetic landscapes, and commonly exploit the chromatin regulatory machinery to enforce oncogenic gene expression programs[1].

Editorial Summary

Brd4 target in acute myeloid leukaemia

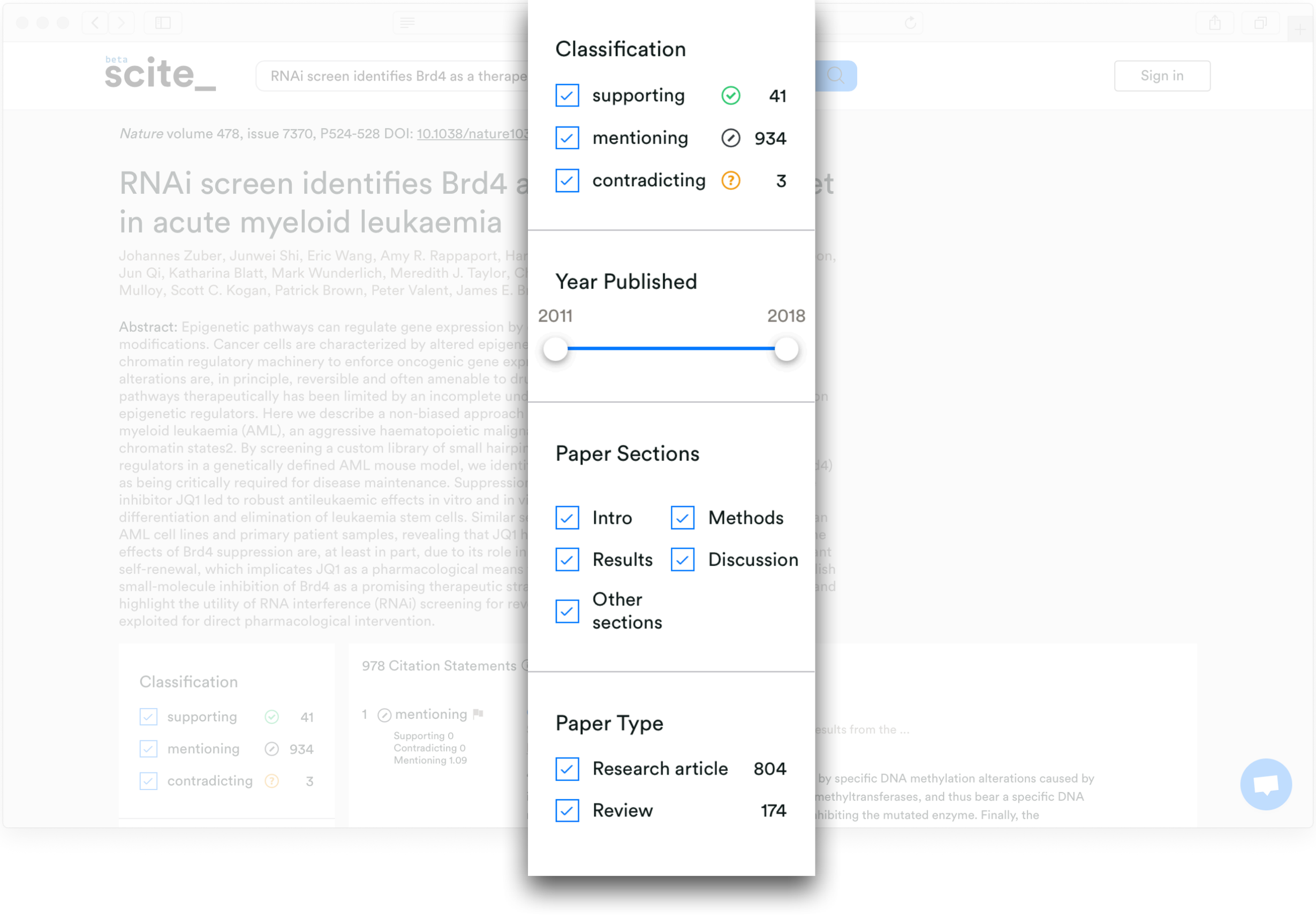
In an RNAi screen targeting chromatin regulators, Vakoc and colleagues find that maintenance of acute myeloid leukaemia (AML) requires... show more

Nature volume 478, issue 7370, P524-528 DOI: 10.1038/nature10334

RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia

Johannes Zuber, Junwei Shi, Eric Wang, Amy R. Rappaport, Harald Herrmann, Edward A. Sison, Daniel Magoon, Jun Qi, Katharina Blatt, Mark Wunderlich, Meredith J. Taylor, Christopher Johns, Agustin Chicas, James C. Mulloy, Scott C. Kogan, Patrick Brown, Peter Valent, James E. Bradner, Scott W. Lowe, Christopher R. Vakoc

Abstract: Epigenetic pathways can regulate gene expression by controlling and interpreting chromatin modifications. Cancer cells are characterized by altered epigenetic landscapes, and commonly exploit the chromatin regulatory machinery to enforce oncogenic gene expression programs1. Although chromatin alterations are, in principle, reversible and often amenable to drug intervention, the promise of targeting such pathways therapeutically has been limited by an incomplete understanding of cancer-specific dependencies on epigenetic regulators. Here we describe a non-biased approach to probe epigenetic vulnerabilities in acute myeloid leukaemia (AML), an aggressive haematopoietic malignancy that is often associated with aberrant chromatin states2. By screening a custom library of small hairpin RNAs (shRNAs) targeting known chromatin regulators in a genetically defined AML mouse model, we identify the protein bromodomain-containing 4 (Brd4) as being critically required for disease maintenance. Suppression of Brd4 using shRNAs or the small-molecule inhibitor JQ1 led to robust antileukaemic effects in vitro and in vivo, accompanied by terminal myeloid differentiation and elimination of leukaemia stem cells. Similar sensitivities were observed in a variety of human AML cell lines and primary patient samples, revealing that JQ1 has broad activity in diverse AML subtypes. The effects of Brd4 suppression are, at least in part, due to its role in sustaining Myc expression to promote aberrant self-renewal, which implicates JQ1 as a pharmacological means to suppress MYC in cancer. Our results establish small-molecule inhibition of Brd4 as a promising therapeutic strategy in AML and, potentially, other cancers, and highlight the utility of RNA interference (RNAi) screening for revealing epigenetic vulnerabilities that can be exploited for direct pharmacological intervention.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Nature volume 478, issue 7370, P524-528 DOI: 10.1038/nature103
RNAi screen identifies Brd4 a
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Contradicting 0.5
Mentioning 0.17

BRD4 Connects Enhancer Remodeling to Senescence Immune Surveillance

Tasdemir et al. 2016

Cancer Discovery Section: Discussion

Full Text

"...Our data linking BRD4 to a tumor suppressive program stands in apparent contrast to the established role of BRD4 in tumors as a cancer maintenance gene (*39*, ***53***, *68*). Still, consistent with a potential role for BRD4 in other tumor suppressive programs, BRD4 inhibition can enhance oncogenic dedifferentiation in human breast cancer cells and cells from premature aging syndrome patients (*69*, *70*), and promotes hyperproliferation in the murine epidermis (*71*)...."

contradicting

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Mentioning 0.33

BET Bromodomains Mediate Transcriptional Pause Release in Heart Failure

Anand et al. 2013

Cell Section: Discussion

Full Text

"...GSEA reveals that BET inhibition antagonizes multiple TF outputs known to be causal in HF pathogenesis including NFAT, NFκB and GATA4, suggesting that BET bromodomain proteins co-activate a broad transcriptional network involving multiple TFs. Importantly, we find that BET bromodomain proteins do not directly affect Myc mRNA levels or function in the heart – a striking contrast to observations in hematopoietic tumors, where BETs are required for c-Myc expression and activity (*Delmore et al, 2011*; ***Zuber et al, 2011***). ChIP-seq analysis reveals that BRD4 co-occupies active promoters with Pol II (as defined by H3K4me3), and active gene enhancers (as defined by H3K27ac) in the adult mouse heart and that cardiac pressure overload induces Pol II pause release and transcriptional elongation within four days...."

S_

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duplication cycle (Holland and Cleveland, 2009; Thompson and Compton, 2010).

Studies carried out primarily in yeast and mammalian cell lines have shown that aneuploidy comes with a fitness cost. Aneuploid cells typically grow slower (McCoy *et al.*, 1974; Torres *et al.*, 2007; Williams *et al.*, 2008; Tang *et al.*, 2011; Siegel and Amon, 2012; Stingele *et al.*, 2012) and suffer from replication stress that leads to DNA damage and gene mutation (Janssen *et al.*, 2011; Crasta *et al.*, 2012; Santaguida and Amon, 2015a; Passerini *et al.*, 2016; Ly and Cleveland, 2017). Also, both in vitro engineered aneuploid cells and chromosomally unstable cancer cells display gene expression patterns (Sheltzer, 2013) reminiscent of stress responses first described in yeast (Gasch, 2007). Accordingly, aneuploid cells were found to show increased sensitivity toward compounds inducing energy stress and proteotoxic stress (Tang *et al.*, 2011). In nontransformed cells, chromosome missegregation generally leads to p53-dependent cell cycle arrest and, ultimately, cell death (Li *et al.*, 2010; Thompson and Compton, 2010; Uetake and Sluder, 2010; Janssen *et al.*, 2011; Lambrus *et al.*, 2016). Yet, despite this fitness cost, severe aneuploidy and CIN are hallmarks of human cancers (Hanahan and Weinberg, 2011; Holland and Cleveland, 2012; Funk *et al.*, 2016; De Braekeleer *et al.*, 2017). They contribute to increased transformative potential (Paulsson and Johansson, 2007; Weaver *et al.*, 2007) and correlate with poor prognosis (McGranahan *et al.*, 2012). To resolve this apparent conundrum, it is generally argued that aneuploidy and CIN result in deregulated gene expression, which then confers a selective advantage during the evolution of a tumor in a changing microenvironment (Baek *et al.*, 2009; Pavelka *et al.*, 2010; Kwon-Chung and Chang, 2012; Yona *et al.*, 2012). As one example supporting this notion, DLD-1 cells engineered to carry single-chromosome aneuploidies were found to have a selective advantage over diploid control cells when cultured under non-standard conditions, such as serum starvation, drug treatment, or hypoxia (Rutledge *et al.*, 2016). Such observations, as well as data obtained in tumor models, strongly support the hypothesis that aneuploidy is not a by-product of cell transformation but, when present at appropriate levels, contributes to tumor development (Hanks *et al.*, 2004; Holland and Cleveland, 2012; Davoli *et al.*, 2013).

Aneuploidy in cancer cells may arise when diploid progenitors gain or lose individual chromosomes. However, chromosome loss is not well tolerated in diploid cells (Alvaro *et al.*, 2006; Anders *et al.*, 2009). Moreover, cancer cells often carry near-tetraploid chromosome numbers, indicative of whole genome duplication events (Zack *et al.*, 2013). This suggests that aneuploid cancer cells often derive from tetraploid intermediates (Cowell and Wigley, 1980; Mayer and Aguilera, 1990; Storchova and Pellman, 2004; Storchova and Kuffer, 2008; Holland and Cleveland, 2012). Considering that tetraploidization creates redundancy in chromosome content, it is expected to protect descendant aneuploid cells from the negative effects of haploinsufficiency (Shackney *et al.*, 1989; Storchova and Pellman, 2004; Ganem and Pellman, 2007; Thompson and Compton, 2010; Dewhurst *et al.*, 2014).

Aneuploidy has traditionally been ascribed to defects in mitotic spindle organization and/or dysfunction of the spindle assembly checkpoint (Wang *et al.*, 2007; Kops *et al.*, 2005). However, although mutations in spindle checkpoint genes can indeed cause aneuploidy (Hanks *et al.*, 2004; Yost *et al.*, 2017), such mutations have not been commonly observed in cancers (Cahill *et al.*, 1999; Haruki *et al.*, 2001). Deregulated expression of essential regulators of chromosome segregation and cell division has been observed in cancers with high degrees of aneuploidy and, accordingly, a CIN marker signature (CIN70) was proposed (Carter *et al.*, 2006). However, subsequent studies argued that this CIN signature reflects altered proliferation rate rather than chromosome missegregation (Venet *et al.*, 2011; Sheltzer, 2013; Buccitelli *et al.*, 2017). Thus, a specific cellular response to CIN has not yet been identified.

Here we established a set of transformed cancer cell lines of isogenic origin but differing in chromosome content and propensity to chromosome missegregation. To determine the effects of gains in chromosome mass *versus* CIN on protein expression and phosphorylation, we subjected the different cell lines to extensive proteomic and phosphoproteomic analyses. We found that proteomic changes in response to CIN are similar to those observed in response to tetraploidy and are more readily detectable at the level of protein phosphorylation than at the level of protein expression. Furthermore, our results indicate that large gains in chromosome number, as caused by tetraploidization, trigger widespread responses in protein expression and phosphorylation patterns, lending support to the notion that an initial genome doubling event can set the stage for survival and propagation of descendent aneuploid tumor cells.

RESULTS

Establishment of DLD-1–derived cell lines differing in ploidy and aneuploidy

Chromosome gains or losses result in massive changes in gene expression (Lyle *et al.*, 2004; Upender *et al.*, 2004; Stingele *et al.*, 2012), and protein expression patterns in cancer cell lines are known to reflect tissue origin, a priori making it difficult to identify a proteomic signature attributable to CIN. This notwithstanding, we subjected a panel of human cell lines to a proteomic quantification based on multiplexed tandem mass tag (TMT) labeling, a method of choice for achieving high proteome coverage in multiple samples and within a reasonable time frame (Thompson *et al.*, 2003; Ahrne *et al.*, 2016)(Supplemental Figure S1A and Supplemental Table S1). This panel included seven karyotypically stable (nonCIN) and unstable (CIN) cancer cell lines originating from different tumor tissues (Gascoigne and Taylor, 2008) and the immortalized retinal cell line hTERT. In line with previous data (Gascoigne and Taylor, 2008), we found that differences in global protein expression patterns were too profound to allow a distinction between CIN and karyotypically stable (nonCIN) cell lines through hierarchical cluster analysis (Supplemental Figure S1B). Nevertheless, this pilot study showed that our proteomics approach allowed for reliable quantification of thousands of proteins in each cell line.

To reduce interline variation due to tissue origin, we next used the diploid colon cancer cell line DLD-1 to generate descendant lines differing in karyotype. DLD-1 cells show microsatellite instability (MIN) but proliferate in a near-diploid state (Lengauer *et al.*, 1997). As DLD-1 cells are deficient in p53, tetraploid derivatives can readily be established through inhibition of cytokinesis (Dresdopoulos *et al.*, 2014). This afforded a syngeneic pair of stable diploid and tetraploid cells (Figure 1A). Starting with a culture of tetraploid DLD-1 cells, we then used single cell fluorescence-activated sorting (FACS) to isolate spontaneously arising aneuploid descendants. This provided us with four different PTA clones, specifically three near-triploid lines and one near-tetraploid line (Figure 1B). Finally, we applied microcell-mediated chromosome transfer (Stingele *et al.*, 2012) to the parental diploid DLD-1 culture and obtained two viable trisomic clones carrying three copies of chromosome 7 (Tr 7) (Figure 1B). For all cell lines, DNA content was confirmed by chromosome counting (Figure 1C) and chromosome painting (Supplemental Figure S2A). This collection of isogeneic cell lines set the stage for analyzing chromosomally stable diploid,

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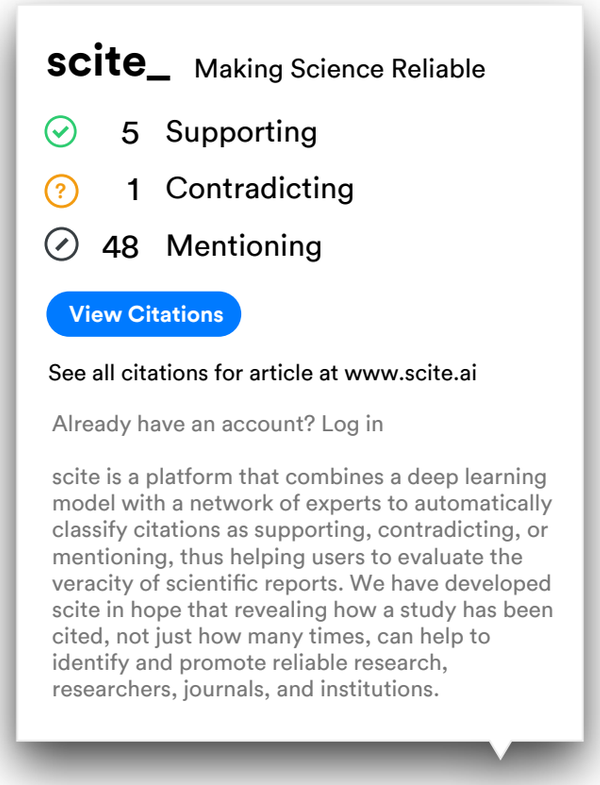

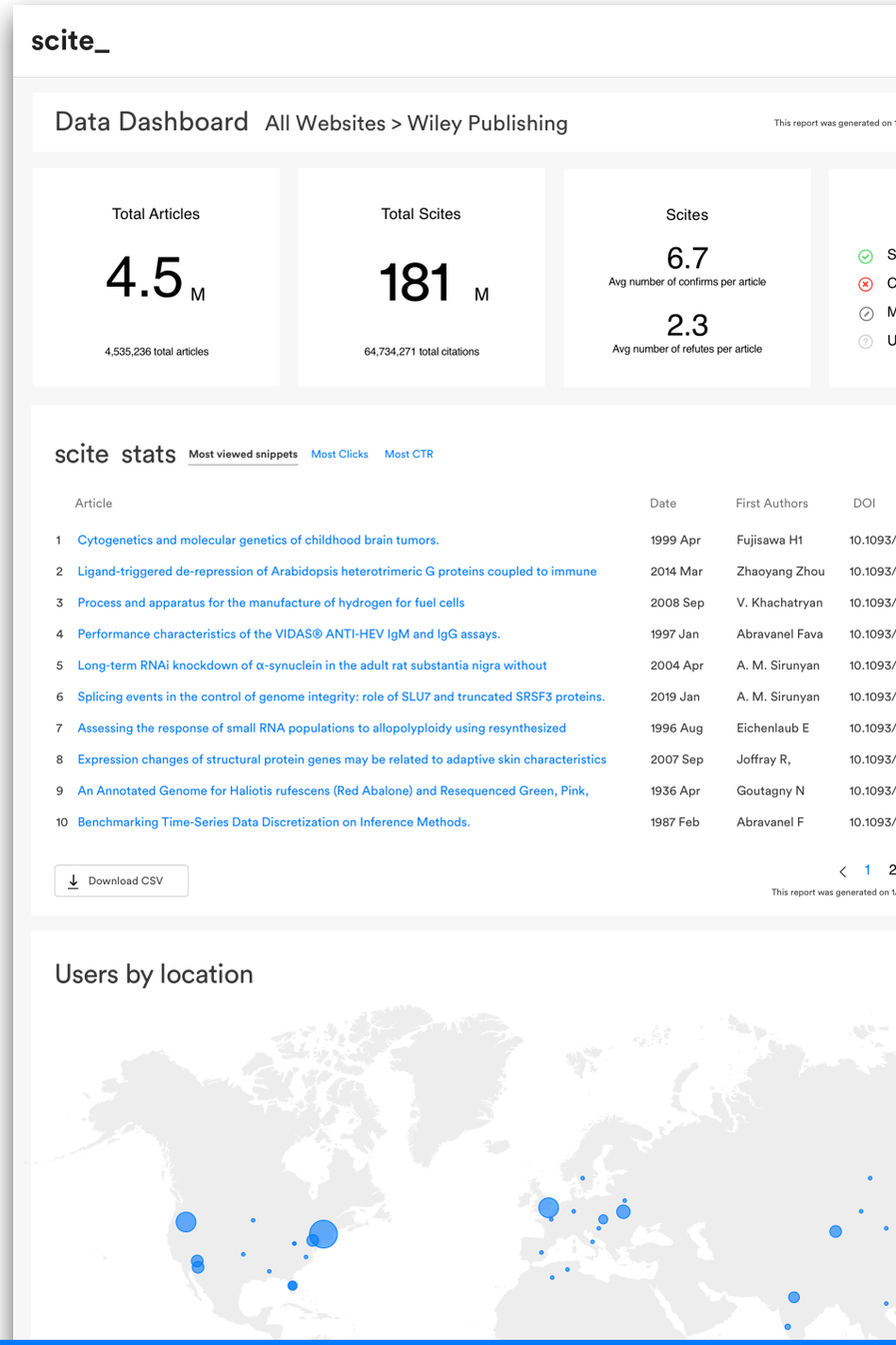

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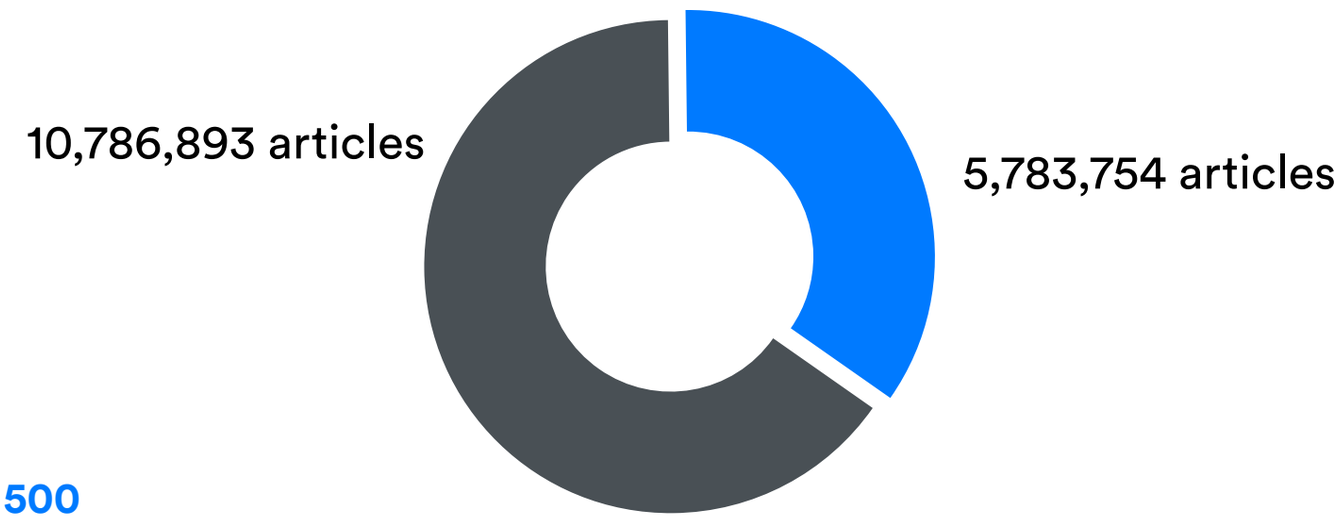

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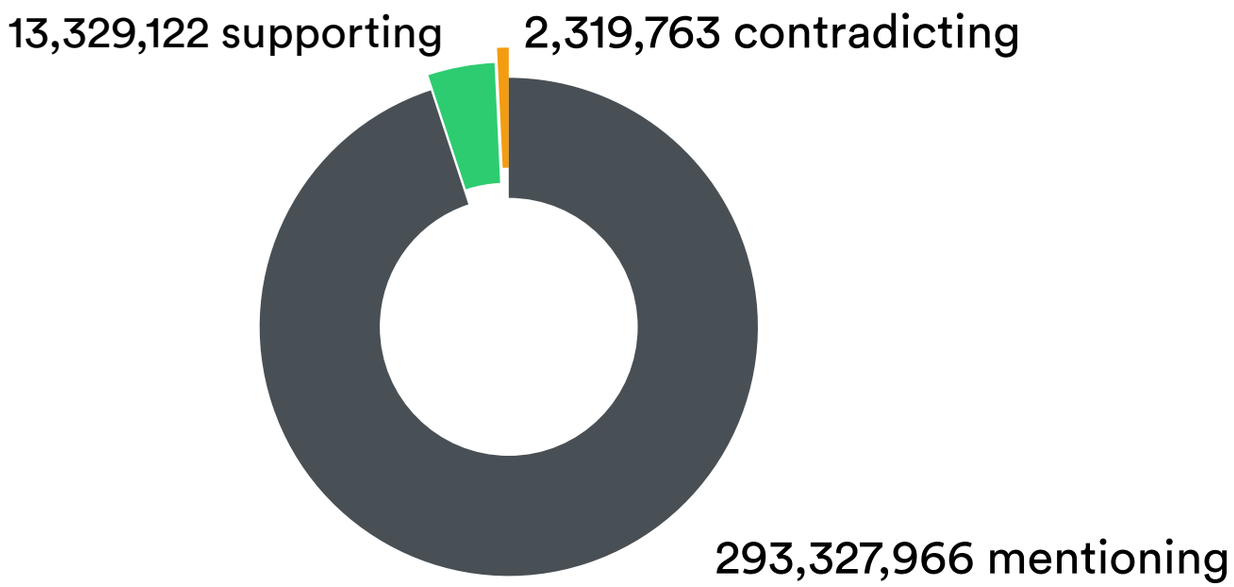

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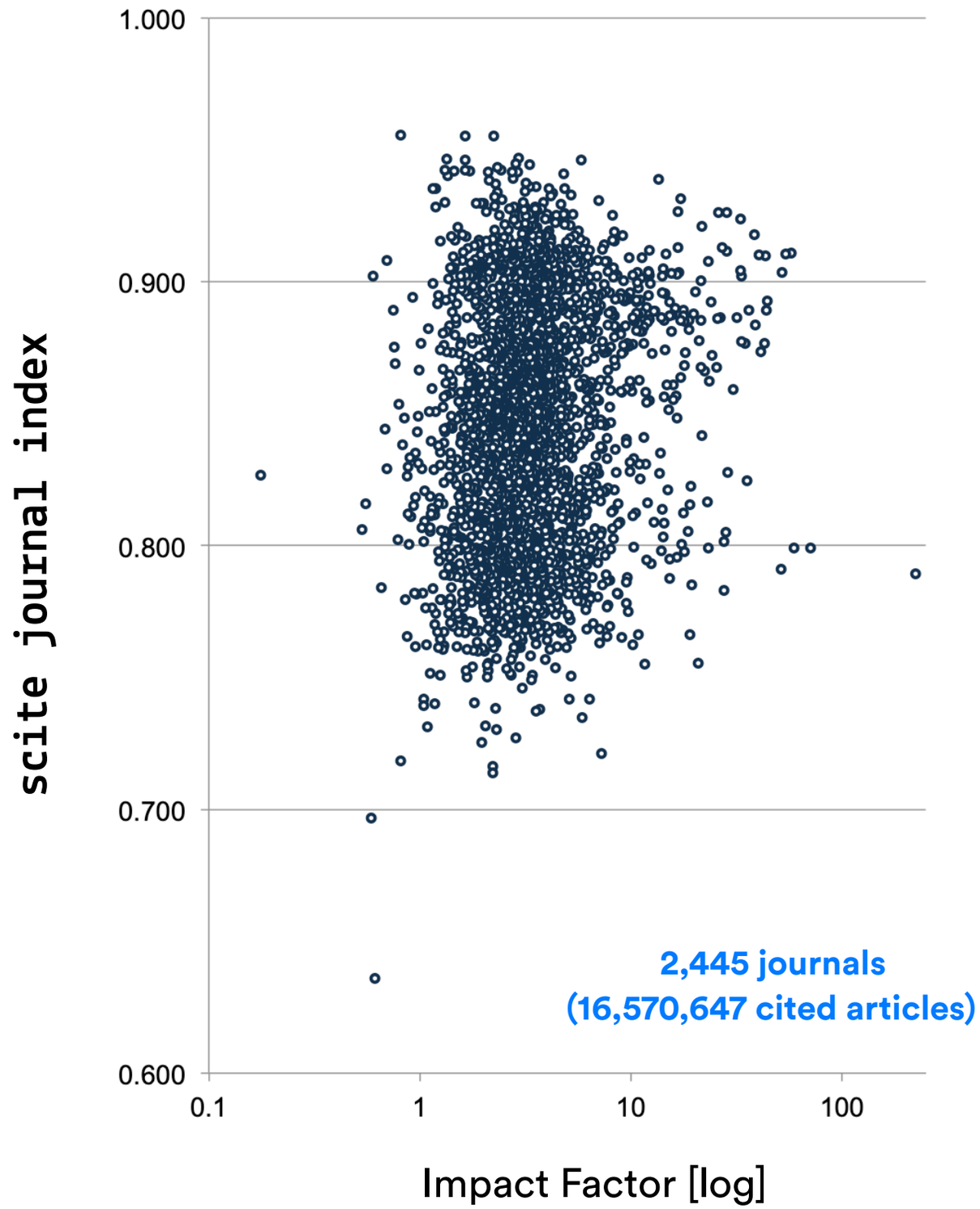

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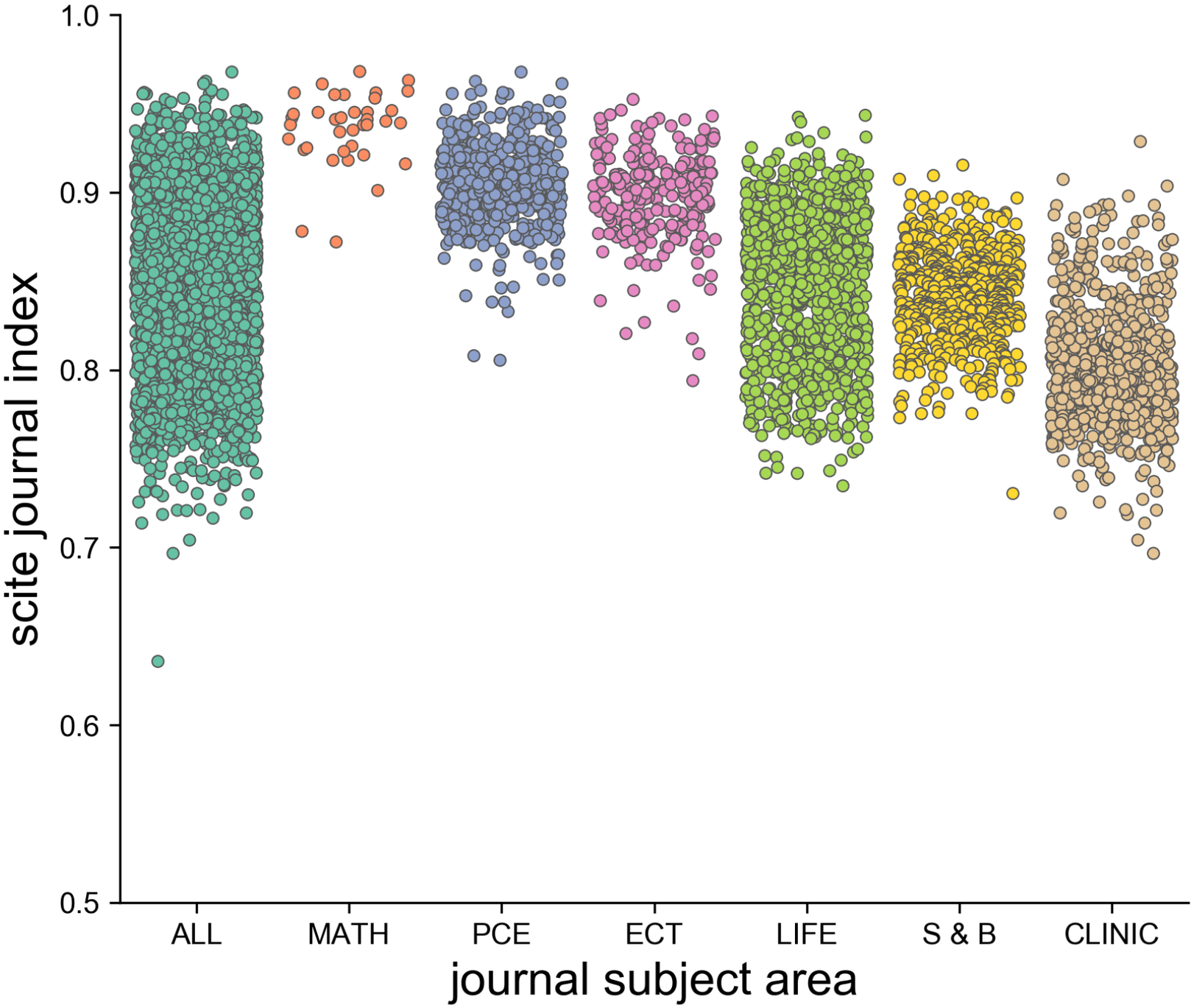

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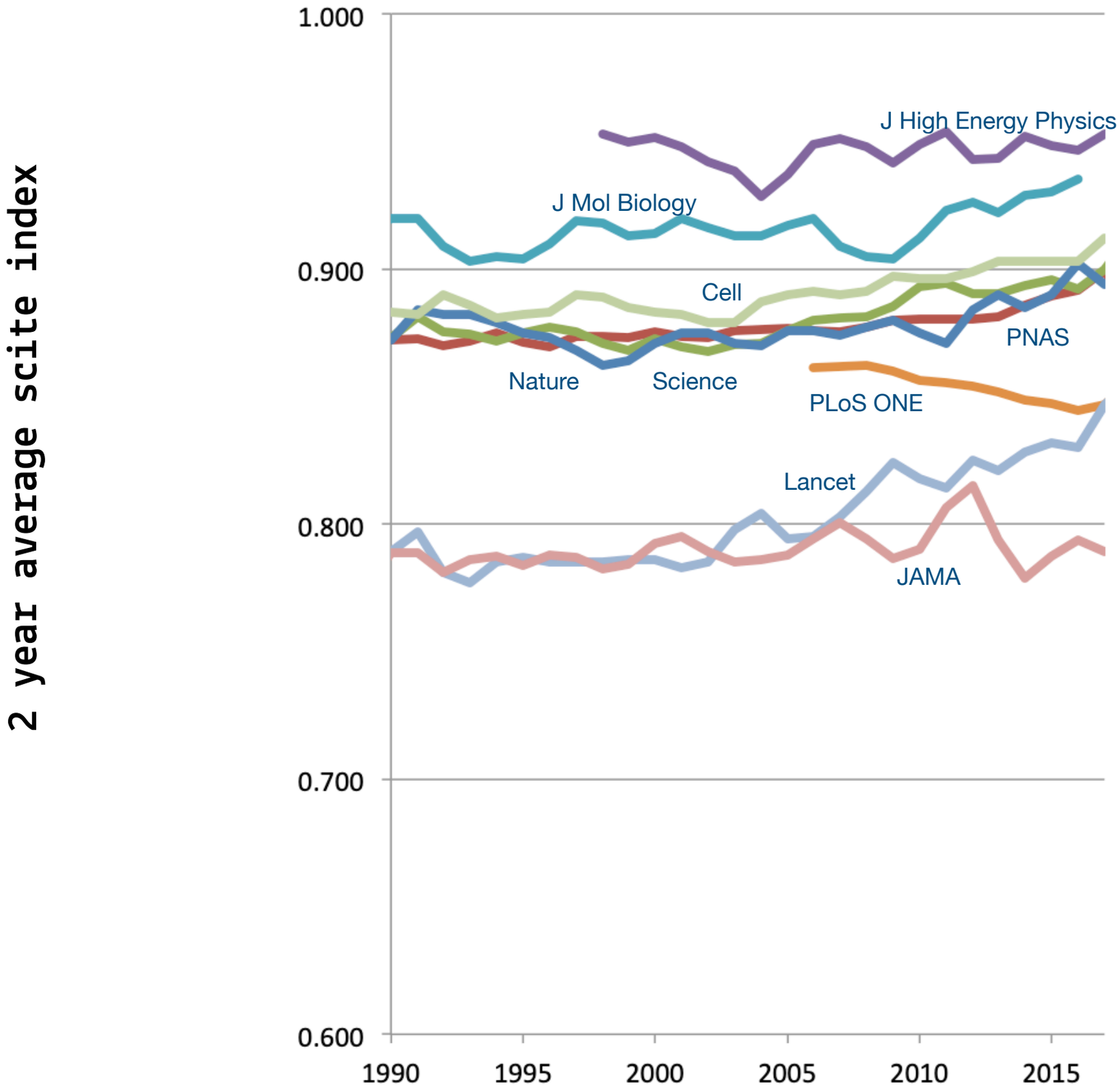

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Thank you!

Josh Nicholson PhD,
CEO

two-time CEO (The Winnower,acquired 2016; Authorea, acquired 2018)

PhD in cancer research from Virginia Tech

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has managed teams of developers, designers, marketers, and salespeople, to produce products used by hundreds of thousands of researchers from leading institutions around the world.

Milo Mordaunt,
CTO

BA in Classics from Cambridge University (network theory and text mining of Homer's Odyssey)

full stack developer with over 13 years of experience

has developed numerous products across industries

Yuri Lazebnik PhD,
CSO

PhD in biochemistry from St. Petersburg University

three decades of cancer research, two decades as a PI at Cold Spring Harbor Laboratory

author of 52 research papers

wealth of connections in academia and industry

produced and licensed reagents to industry.

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PhD in Computer Science from Henri Poincaré (France)
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research focuses on the application of machine-learning algorithms to social science research of social networks

Funded in part by the National Science Foundation and the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH).

Thank you!

Josh Nicholson PhD, CEO

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