



Content Innovation

Increasing research efficiency

Lucia Franco

15 April 2010

Content Innovation – A Journey

- Article of the Future
 - Why, How, What
 - Cell Press case
 - Feedback
 - Other disciplines
- Contextual Linking



Content Innovation – A Journey

- Article of the Future

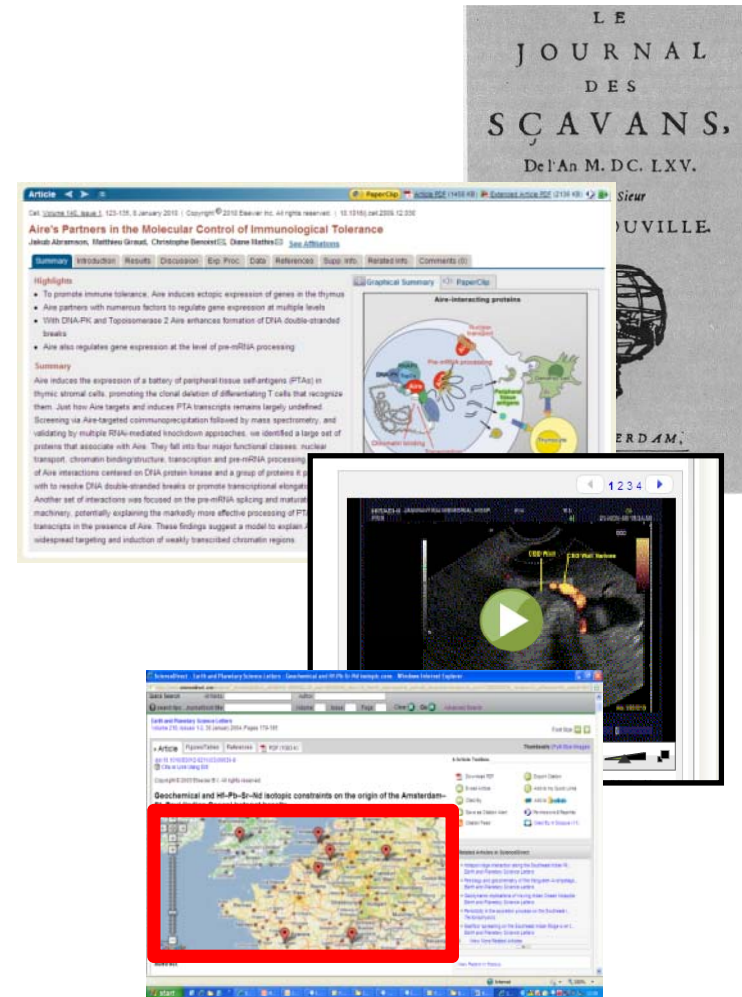
- Why, How, What

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Elsevier Article of the Future project

- Why: increase efficiency of the scientist
 - Faster understanding and digestion of article
 - Easier execution of tasks related to the article
- How: provide discipline-specific value to article
 - Different disciplines have different needs and tasks
 - Integration with / and interconnecting to other research
 - Match with workflow behaviour
- What:
 - Article format / presentation
(semantics is a different project)
 - Exploit web-technology capabilities
 - In collaboration with scientific community

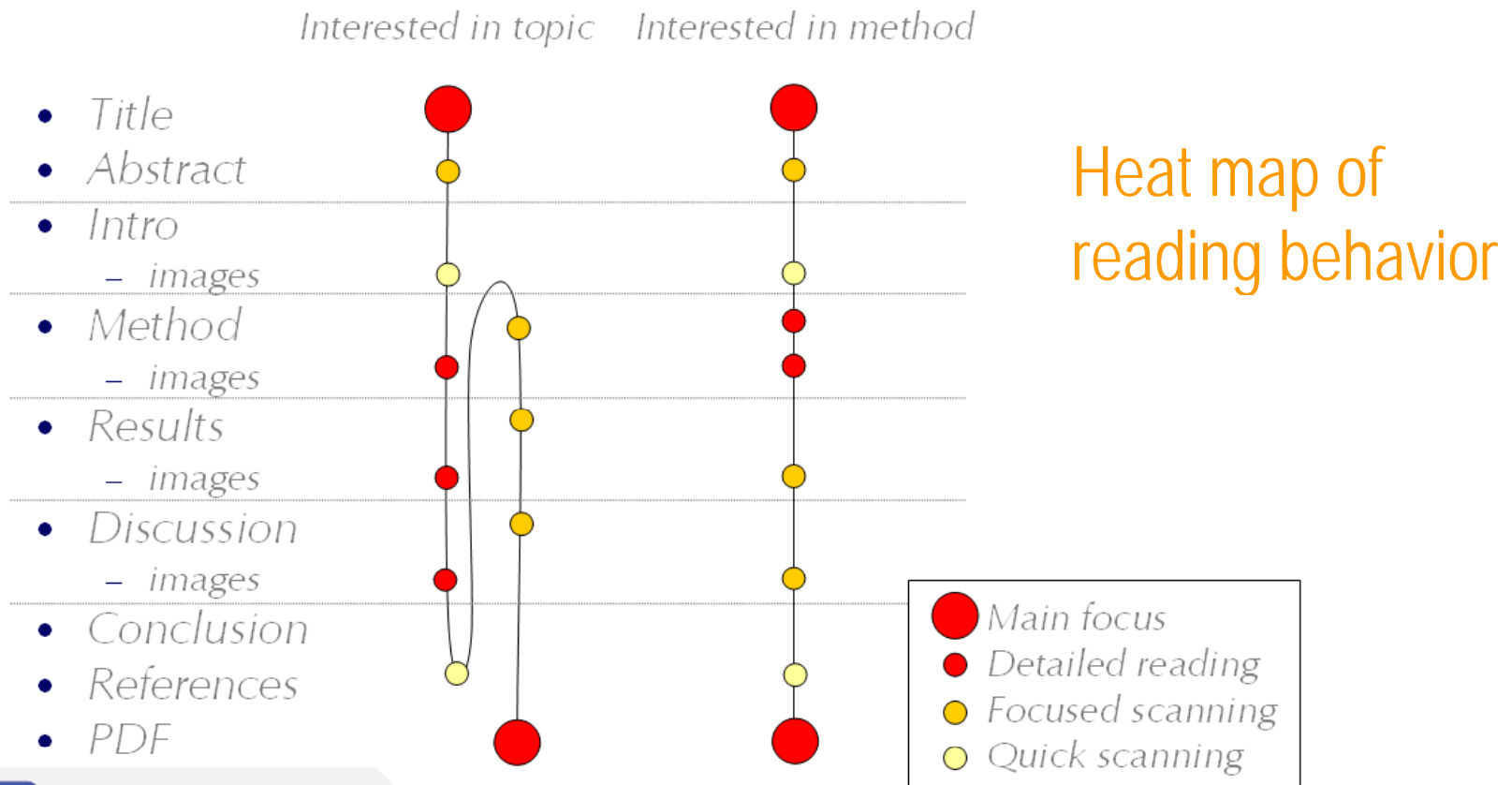
Content Innovation – A Journey

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Article of the Future: Cell Press

- July 2009: Cell Press AotF prototype went public
- January 2010: Cell Press AotF production (cell.com)



Tabbed view for quick support of tasks

Article

PaperClip

Article PDF (1458 KB)

Extended Article PDF (2136 KB)

Cell, Volume 140, Issue 1, 123-135, 8 January 2010 | Copyright © 2010 Elsevier Inc. All rights reserved. | 10.1016/j.cell.2009.12.030

Aire's Partners in the Molecular Control of Immunological Tolerance

Idit Abramson, Matthieu Girard, Christophe Benoist, Diane Mathis

Summary

Introduction

Results

Discussion

Exp. Proc.

Data

References

Supp. Info.

Related Info.

Comments (0)

Highlights

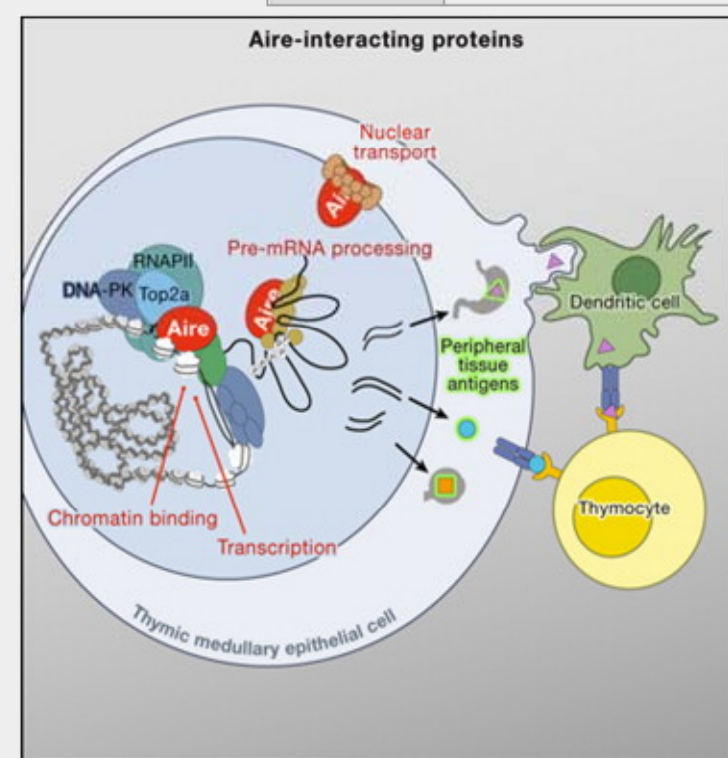
- To promote immune tolerance, Aire induces ectopic expression of genes in the thymus
- Aire partners with numerous factors to regulate gene expression at multiple levels
- With DNA-PK and Topoisomerase 2 Aire enhances formation of DNA double-stranded breaks
- Aire also regulates gene expression at the level of pre-mRNA processing

Summary

Aire induces the expression of a battery of peripheral-tissue self-antigens (PTAs) in thymic stromal cells, promoting the clonal deletion of differentiating T cells that recognize them. Just how Aire targets and induces PTA transcripts remains largely undefined. Screening via Aire-targeted coimmunoprecipitation followed by mass spectrometry, and validating by multiple RNAi-mediated knockdown approaches, we identified a large set of proteins that associate with Aire. They fall into four major functional classes: nuclear transport, chromatin binding/structure, transcription and pre-mRNA processing. One set of Aire interactions centered on DNA protein kinase and a group of proteins it partners with to resolve DNA double-stranded breaks or promote transcriptional elongation. Another set of interactions was focused on the pre-mRNA splicing and maturation machinery, potentially explaining the markedly more effective processing of PTA transcripts in the presence of Aire. These findings suggest a model to explain Aire's widespread targeting and induction of weakly transcribed chromatin regions.

Graphical Summary

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Research highlights with key results

Article

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Aire's Partners in the Molecular Control of Immunological Tolerance

Jakub Abramson, Matthieu Giraud, Christophe Benoist, Diane Mathis [See Affiliations](#)

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Highlights

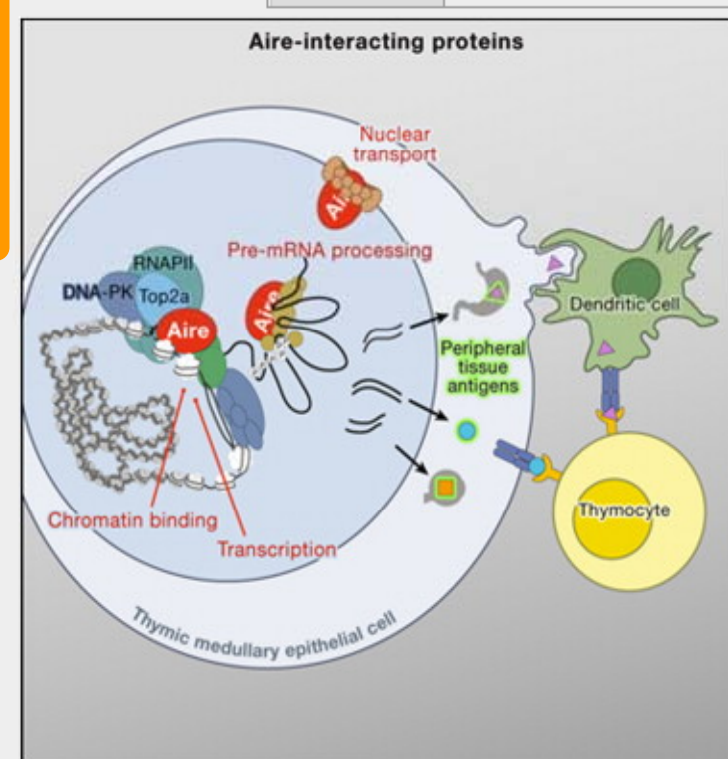
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Graphical Summary

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Graphical abstract with main message

Article

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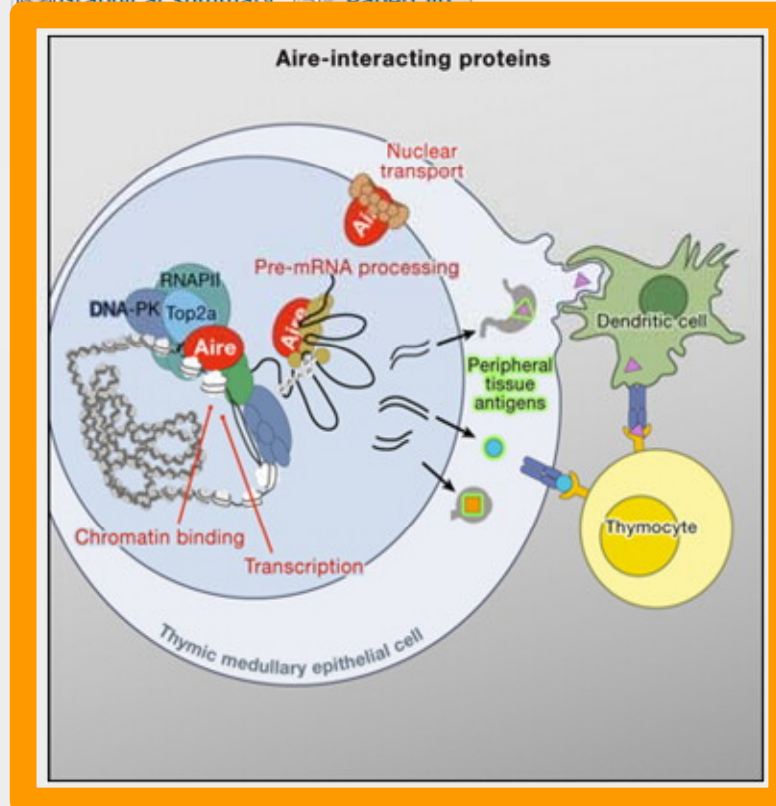
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Graphical Summary

PaperClip



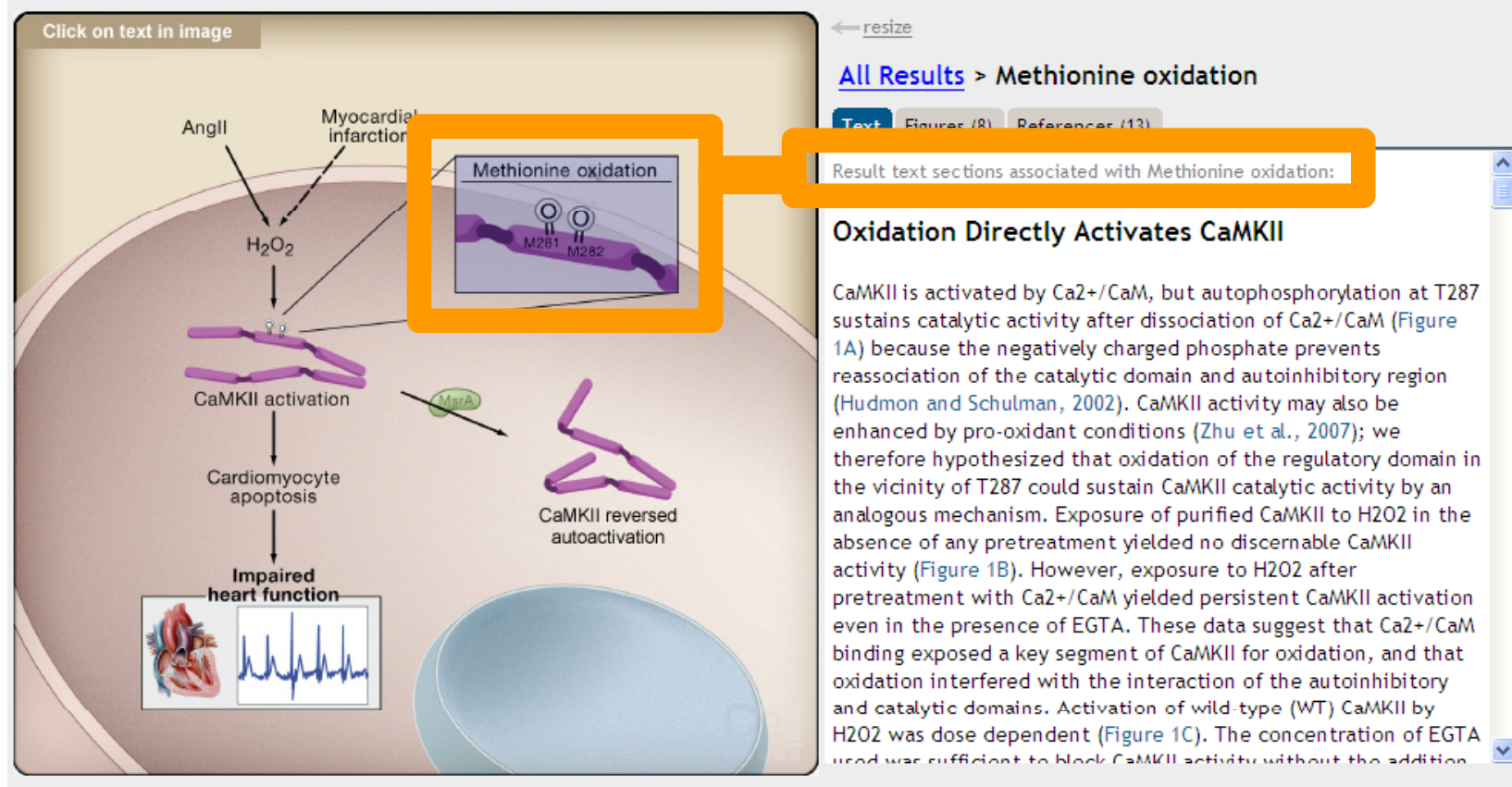
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May 2, 2008 - Volume 133, Issue 3, pp. 462-474  PDF (1,758 KB)

A Dynamic Pathway for Calcium-Independent Activation of CaMKII by Methionine Oxidation

Jeffrey R. Erickson¹, Mei-ling A. Joiner¹, Xiaoqun Guan¹, William Kutschke¹, Jinying Yang¹, Carmine V. Oddis⁵, Ryan K. Bartlett⁶, John S. Lowe¹, Susan E. O'Donnell², Nukhet Aykin-Burns³, Matthew C. Zimmerman³, Kathy Zimmerman⁹, Amy-Joan L. Ham^{7,8}, Robert M. Weiss^{1,9}, Douglas R. Spitz³, Madeline A. Shea², Roger J. Colbran⁷, Peter J. Mohler^{1,4}, and Mark E. Anderson^{1,4,*} [Affiliations](#)

[Abstract](#) [Introduction](#) [Results](#) [Discussion](#) [Experimental Procedures](#) [Figures \(8+\)](#) [References \(51\)](#) [Authors](#) [Comments \(3\)](#) [Acknowledgements](#)



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Biological and Molecular Heterogeneity of Breast Cancers Correlates with Their Cancer Stem Cell Content

Salvatore Pece, Daniela Tosoni, Stefano Confalonieri, Giovanni Mazzarol, Manuela Vecchi, Simona Ronzoni, Loris Bernard, Giuseppe Viale, Pier Giuseppe Pelicci, Pier Paolo Di Fiore [See Affiliations](#)

Summary Introduction Results Discussion Exp. Proc. **Data** References Supp. Info. Related Info. Comments (0)

Figures (1) Excel (2)

Figure 1 Figure 2 Figure 3 Figure 4 Figure 5 Figure 6 Figure S1 Figure S2 Figure S3 Figure S4

A Bright field PKH26 Merge

B Cumulative sphere number (5,000 cells plated) Passages

C Cumulative sphere number (2,500 PKH^{POS} cells plated) Passages

D 0 h 30 h

E BrdU PKH26 Ki67 PKH26 100 PKH^{POS}

Caption Context in Article

Supplemental Figure S1: Purification of hNMSCs

(A) A mammosphere derived from PKH26-labeled epithelial cells. The scale bar represents 100 μ m.

(B and C) Propagation of mammospheres for multiple generations starting from bulk epithelial cells (B, open and closed circles indicate two different patients) or FACS-sorted PKH^{POS} cells (C). Top, linear scale; bottom, semilog scale. Regression analysis trend lines and coefficients (R^2) are shown. Typical experiments, in triplicate, are shown (additional statistical analyses are in Figures S1B and S1C).

(D) A single PKH^{POS} cell, embedded in methylcellulose, was monitored

Article [Article PDF \(1805 KB\)](#) [Extended Article PDF \(3763 KB\)](#)

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Figures (1) Excel (2)

Figure 1 [Figure 2](#) [Figure 3](#) [Figure 4](#) [Figure 5](#) [Figure 6](#) [Figure S1](#) [Figure S2](#) [Figure S3](#) [Figure S4](#)

A Bright field PKH26 Merge

B Cumulative sphere number (5,000 cells plated) Passages $R^2 = 0.99$ $R^2 = 1$

C Cumulative sphere number (2,500 PKH^{POS} cells plated) Passages $R^2 = 0.99$

D 0 h 30 h

E BrdU PKH26 Ki67 PKH26 100 PKH^{POS}

Caption **Context in Article**

Cells from normal human mammary glands were labeled with PKH26 and plated in suspension to allow mammosphere growth (Figure S1A available online). As expected, very few cells within mammospheres retained strong epifluorescence (Figure 1A). The sphere-forming efficiency (SFE) of cells from the mammary gland was 0.003%–0.01% (depending on whether bulk mammary cells or pre-enriched mammary epithelial cells were employed, Figure S1B). The SFE of cells obtained from dissociated mammospheres was ~0.1% (F2 in Figure S1B). Normal mammospheres could be propagated for at least four generations (Figure 1B), and their clonogenic ability decreased exponentially (Figure 1B, Figure S1C): at every generation, the SFE was ~23% of that measured in the preceding generation (Figure

Simultaneous view of text, figures, and caption

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Data

References

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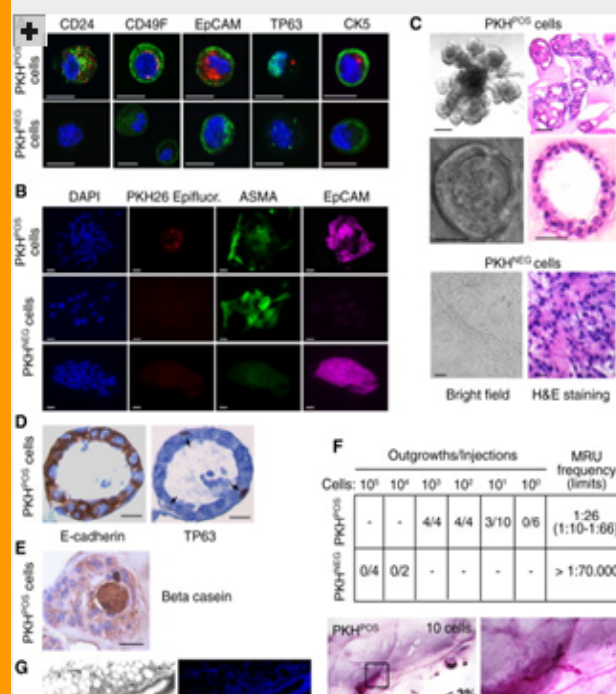
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efficiency of around 4% (one in 26 cells, range 1:10–66), while PKH^{NEG} cells could not reconstitute the mammary gland, even when injected at concentrations as high as 10⁵ cells/transplant (Figure 2F). Of note, this value is compatible with the maximum expected value of reconstitution, estimated on the basis of the replicative kinetics of PKH^{POS} cells (Figure S1E). The outgrowths generated by PKH^{POS} cells displayed the normal mammary gland cytoarchitecture (Figure 2G, Figure S2C) and were derived unequivocally from transplanted human cells (Figure 2G, Figure S2D).

Transcriptomic Analysis of hNMSCs

Click either the + or - icon to get zoom cursor. Click and Hold zoom



or to zoom in or out. The mouse wheel can also be used

Figure 2. Immunophenotypical and Functional Characterization of PKHPOS and PKHNEG Cells

(A) PKH^{POS} or PKH^{NEG} cells were analyzed with the indicated antibodies by IF. Green, antibody staining; red, PKH26 epifluorescence; blue, DAPI. Scale bars represent 10 μ m. Quantification is shown in Figure S2A. Results are typical and representative of three independent experiments.

(B) PKH^{POS} or PKH^{NEG} cells were grown on Matrigel and analyzed in IF with the indicated antibodies. Scale bars represent 10 μ m. Quantification is

References: context and filtering

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Filter References By Year:

Related Info. Comments (0)

Year	Title	Source
2008	Ben-Porath, I., Thomson, M.W., Carey, V.J., Ge, R., Bell, G.W., Regev, A., and Weinberg, R.A. An embryonic stem cell-like gene expression signature in poorly differentiated aggressive human tumors.	Nat. Genet. 40, 499–507.
2008	Carter, W.G., Kaur, P., Gil, S.G., Gahr, P.J., and Wayner, E.A. Distinct functions for integrins alpha 3 beta 1 in focal adhesions and alpha 6 beta 4/bullous pemphigoid antigen in a new stable anchoring contact (SAC) of keratinocytes: relation to hemidesmosomes.	J. Cell Biol. 111, 3141–3154.
1997	Chepko, G., and Smith, G.H. Three division-competent, structurally-distinct cell populations contribute to murine mammary epithelial renewal.	Tissue Cell 29, 239–253.
2009	Cicalese, A., Bonizzi, G., Pasi, C.E., Faretta, M., Ronzoni, S., Giulini, B., Briskin, C., Minucci, S., Di Fiore, P.P., and Pelicci, P.G. The tumor suppressor p53 regulates polarity of self-renewing divisions in mammary stem cells.	Cell 138, 1083–1095.

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- We have previously shown that p53 critically controls the binary fate decision of NMSCs in the mouse mammary gland by influencing the rate of symmetric versus asymmetric self-renewing cell divisions (Cicalese et al., 2009). [View in Article](#)
- We have previously shown that skewing self-renewal division from an asymmetric (one stem → one stem + one progenitor) to a symmetric (one stem → two stems) mode is a

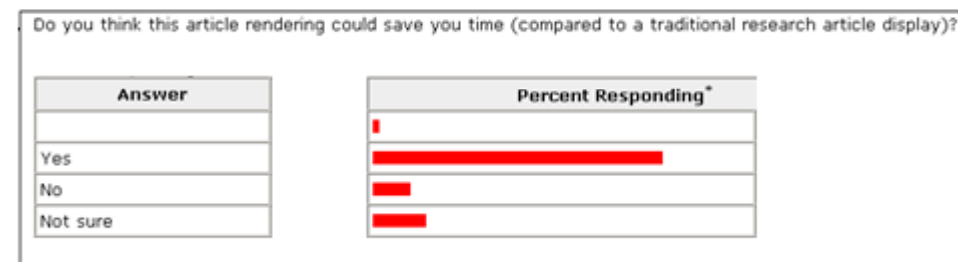
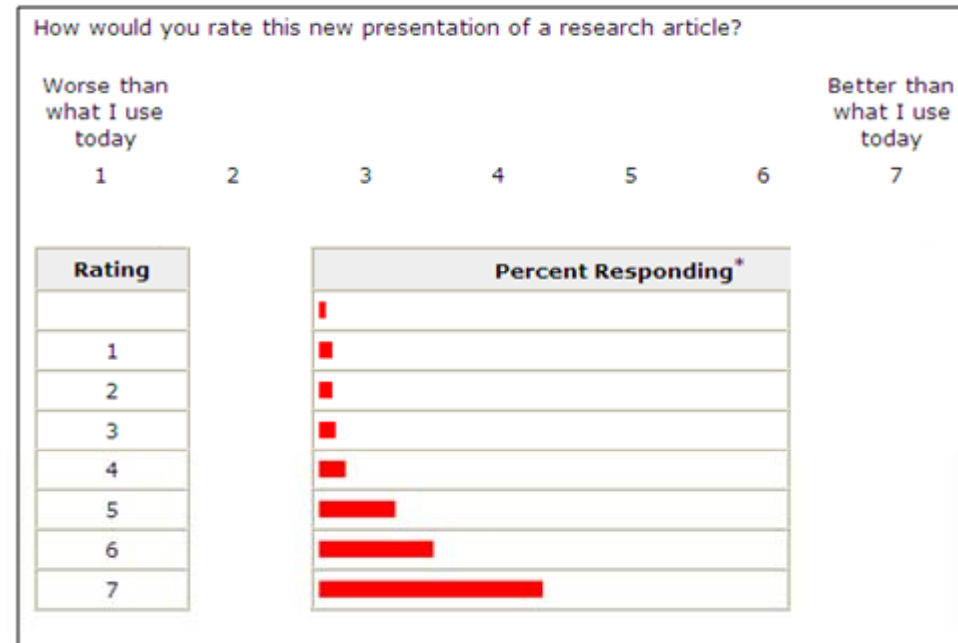
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Results and feedback: Mostly positive

- Survey with > 500 respondents
 - 80% positive
 - 10% neutral
 - 10% negative
- Comments:
 - Fantastic -- wish I thought of it!
 - It looks absolutely amazing.
 - It is simple and practical!
 - More transparent - less scrolling!
 - I like the graphical overviews.
 - Quickly understand concepts.
 - A way to quickly distil the essence.
 - I like "clickable" summary figures.
 - Much-needed change in format.
 - Radically better than what I use



Content Innovation – A Journey

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Article of the Future is domain specific

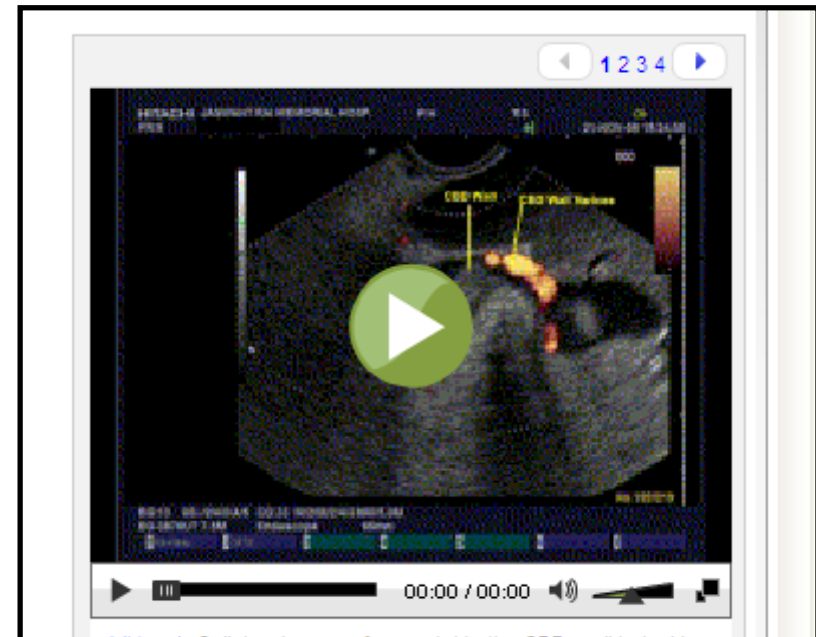
- Follow Cell Press Article-of-the-Future example
- Focus on domain-specific presentation, format, and contents
- Process:
 - Dive into domain specific user needs
 - Define domain specific enhancements for those needs
 - Create domain specific prototype with enhancements
 - Collaborate with domain specific research community via discussion forums and prototype sites
 - Prepare requirements for article production and ScienceDirect
- Beginning with:
 - Chemistry
 - Materials Science
 - Mathematics
 - Psychology
 - Parasitology
 - ...

Article of the Future: preparation

- ScienceDirect must support:
 - 2009: Video
 - 2010: Graphical Abstracts and Research Highlights
 - 2010/11: In-line supplementary data
 - 2011: Tabbed view and figure filmstrip

Streaming inline video

- Increasing use of videos
- In increasing # disciplines
 - Life sciences: cell movements
 - Social sciences: observations
 - Mathematics: explanations
 - Methods and protocols
- ScienceDirect support:
 - Download (from 2002)
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Contains Video1

Description and Demonstration of CBT for ADHD in Adults

Susan E. Sprich^a, Laura E. Knouse^a, Christine Cooper-Vince^a, Jennifer Burbridge^a and Steven A. Safren^a^a Massachusetts General Hospital and Harvard Medical School

Received 31 July 2009; revised 28 August 2009; accepted 1 September 2009. Available online 14 December 2009.

Abstract

ADHD in adulthood is a valid, prevalent, distressing, and interfering condition. Although medications help treat this disorder, there are often residual symptoms after medication treatment, and, for some patients, they are contraindicated. Compared to other disorders, such as mood and anxiety disorders, there are few research-based treatments for this problem. The present article describes a treatment approach to treat ADHD in adults (Safren, Sprich, & Otto, 2005), and for which there is evidence (Safren, Sprich, Penman, & Otto, 2007). To augment the description of treatment, the present article provides video component demonstrations of several core modules that highlight important aspects of this treatment. This description and the accompanying demonstrations are intended as a practical

- Not as supplement but
- ... inline similar to a figure

Supplementary Content within this Article



Video 1. Setting up the calendar system.

[View within Article](#)[Download this Video](#)

Related Articles

- [Cognitive-behavioral therapy for ADHD in medication-treated adults: A review of the literature](#)
Behaviour Research and Therapy
- [The Clinician's Role in the Treatment of ADHD](#)
Clinician's Guide to Adult ADHD
- [History of childhood attention deficit hyperactivity disorder](#)
Journal of Affective Disorders
- [QEEG and neurofeedback for assessment and effective intervention in ADHD](#)
Introduction to Quantitative EEG and Neurofeedback

...can cause the consequences of procrastination and procrastinate because that forgotten task and deadline. The client in the video component mentions that she does not have a consistent system for keeping track of her tasks and often ends up working on lower-priority tasks first and then realizing that she has missed an important task. This gives the therapist the opportunity to reiterate the importance of looking at the task list every day and then he and the client are able to agree on a time when she will do this on a consistent basis (when she first arrives at work each day).



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Setting up the task list. [Video 2.](#)

Problem Solving

"Steve" is a 38-year-old man. At this stage of the treatment, he would have already worked on developing a calendar and task list system and a system for using priority ratings for task list items. The goal of this session is to teach him to use problem solving to deal with items on his task list that are overwhelming or where there is not a clear solution. This session is framed as teaching skills to help with tasks that end up being pushed off from day to day or week to week. When the individual either feels overwhelmed by the task or does not really know how to approach it, avoidance is often the result. Avoidance of difficult or overwhelming tasks often makes the individual feel better in the short-term, but can cause problems in the long-term. As illustrated in the example that follows, the therapist helps the client (a) articulate the problem, (b) generate a list of potential solutions, (c) rate the solutions, and (d) pick the best solution.

Articulate the Problem

[Video clip 3](#) illustrates a situation that we often encounter, where a client gets so overwhelmed and upset by their difficulties that they have a hard time even articulating the problem. The therapist must refocus the discussion on articulating the problem to be solved in a concise manner. After many attempts, during which the client makes self-critical remarks and extreme statements about his situation, the

2010: Graphical Abstracts and Research Highlights

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- ☐ Cell (8)
- ☐ Current Opinion in Cell Biology (4)
- ☐ Biochimica et Biophysica Acta (BBA) - Molecular... (3)
- ☐ Trends in Cell Biology (3)

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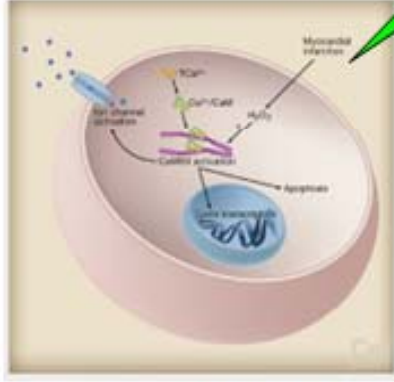
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Seminars in Cell & Developmental Biology, In Press, Corrected Proof, Available online 14 October 2008
Robert N. Kelsh, Melissa L. Harris, Sarah Colanesi, Carol A. Erickson
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2.  **A Dynamic Pathway for Calcium-Independent Activation of Calcium-Induced Mitochondrial Oxidation**
Cell, Volume 133, Issue 3, 2 May 2008, Pages 462-474
Jeffrey R. Erickson, Mei-ling A. Joiner, Xiaoqun Guan, William J. Miller, Jinying Yang, Carmine V. Oddis, Ryan K. Bartlett, John S. Lowe, Susan E. O'Donnell, Nukhet Aykin-Burns, Michael S. Zimmerman, Kathy Zimmerman, Amy-Joan L. Ham, Robert M. Weiss, Douglas R. Spitz, Madeline A. Shea, Peter J. Colbran, Peter J. Mohler, Mark E. Anderson
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Article Highlights

- Oxidation of methionine residues activates CaMKII
- Angiotensin II induces CaMKII oxidation leading to cardiomyocyte death
- CaMKII methionine oxidation is reversed by MsrA
- Elevated CaMKII oxidation impairs heart function and worsens ischemic injury

5.  **Conjugated linoleic acid reduction of murine mammary tumor**
Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology, Volume 1582, Issue 1, 2008, Pages 103-109

Graphical Abstract

Article Highlights

2010/11: In-line supplementary data

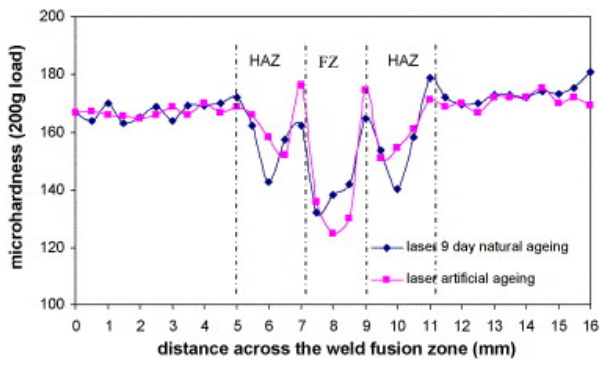
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HAZ was found to decrease with decreasing heat input. In fact autogenous laser welding produced the narrowest HAZ and the results of the micro-hardness of laser weld measurements are shown in Fig. 7.



microhardness (200g load)

distance across the weld fusion zone (mm)

laser 9 day natural ageing

laser artificial ageing

Intracellular Calcium Concentration Measurements

Intracellular calcium concentration was assessed by Fura-2 fluorescence ratio imaging using a microscopic digital imaging system (Photon Technology International), as described previously (Sharma et al., 1995).

Intracellular calcium concentration

Fluorescence Measurements

Spectra were collected at 30 °C using a Fluorolog 3 (Jobin Yvon, Horiba) spectrofluorometer. For intrinsic fluorescence shift experiments, excitation wavelength was 270 nm. Emission spectra were generated at increments from 280 nm to 400 nm. Background traces were subtracted from CaMKII spectra to eliminate contribution from intrinsic fluorescence of CaM. For fluorescence anisotropy experiments, baseline traces of 100 nM dansylated CaM in 15 mM HEPES buffer (pH 7.2) were measured at baseline and after the addition of 200 μM CaCl₂ at 60 s. At 180 s, 100 nM purified CaMKII was added to the CaM solution. For some trials, CaMKII became phosphorylated by the addition of 10 mM ATP. One hundred microliters H₂O₂ or an equivalent volume of buffer was added at 250 s. Finally, addition of 10 mM EGTA at 300 s was used to remove free calcium from the solution, uncoupling CaM/CaMKII binding.

Cardiomyocyte TUNEL Immunostaining

Myocyte isolations from neonatal mouse or rat pups were modified from previously described methods (et al., 2007). To ensure that pure populations of cardiomyocytes were obtained, cultures were immunolabeled with α-actinin Ig (cardiomyocyte-specific marker). Only cultures with > 90% cardiomyocytes were used in

Done

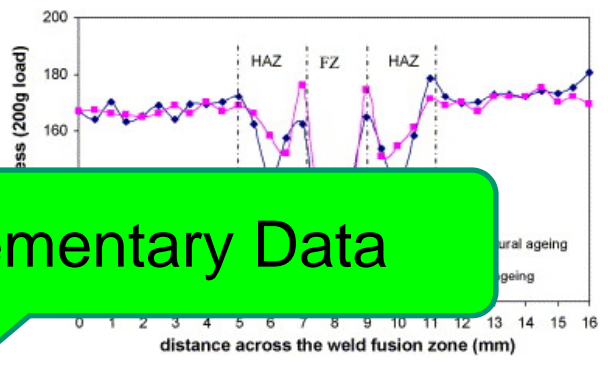
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distance across the weld fusion zone (mm)

laser 9 day natural ageing

laser artificial ageing

Intracellular Calcium Concentration Measurements

Intracellular calcium concentration was assessed by Fura-2 fluorescence ratio imaging using a microscopic digital imaging system (Photon Technology International), as described previously (Sharma et al., 1995).

Intracellular calcium concentration

Intracellular calcium concentration was assessed by Fura-2 fluorescence ratio imaging using a microscopic digital imaging system (Photon Technology International), as described previously (Sharma et al., 1995). Briefly, cultured primary cardiac myocytes were loaded with the Ca²⁺-specific dye Fura-2 by incubating with 1 μM Fura-2/AM (Molecular Probes) at 37 °C for 30 minutes. [Ca²⁺]_i values over the entire cell were calculated from the 340/380-nm ratio images of Fura-2 fluorescence captured before, during and after Iso (100nM) or AngII (100nM) stimulation.

Fluorescence Measurements

Spectra were collected at 30 °C using a Fluorolog 3 (Jobin Yvon, Horiba) spectrofluorometer. For intrinsic fluorescence shift experiments, excitation wavelength was 270 nm. Emission spectra were generated at 1 nm increments from 280 nm to 400 nm. Background traces were subtracted from CaMKII spectra to eliminate the contribution from intrinsic fluorescence of CaM. For fluorescence anisotropy experiments, baseline traces of 100 nM dansylated CaM in 15 mM HEPES buffer (pH 7.2) were measured at baseline and after the addition of 200 μM CaCl₂ at 60 s. At 180 s, 100 nM purified CaMKII was added to the CaM solution. For some trials, CaMKII became phosphorylated by the addition of 10 mM ATP. One hundred microliters H₂O₂ or an equivalent volume of buffer was added at 250 s. Finally, addition of 10 mM EGTA at 300 s was used to remove free

Done

Supplementary Data

2011: Tabbed view and figure filmstrip

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matrix proteins ZDP search SD

Developmental Cell
24 Dec 2009

Article outline

Figures / Tables

Figure 1

Figure 2

Figure 3

Video 1 (1:08)

Related articles

Tools / Applications

Done

A

M F-actin Dyl F-actin Tyn F-actin Zye F-actin

B

M-HRP M-HRP

C

M Dyl M Tyn

Figure 1. ZPD Proteins Localize in Specific Subapical Domains

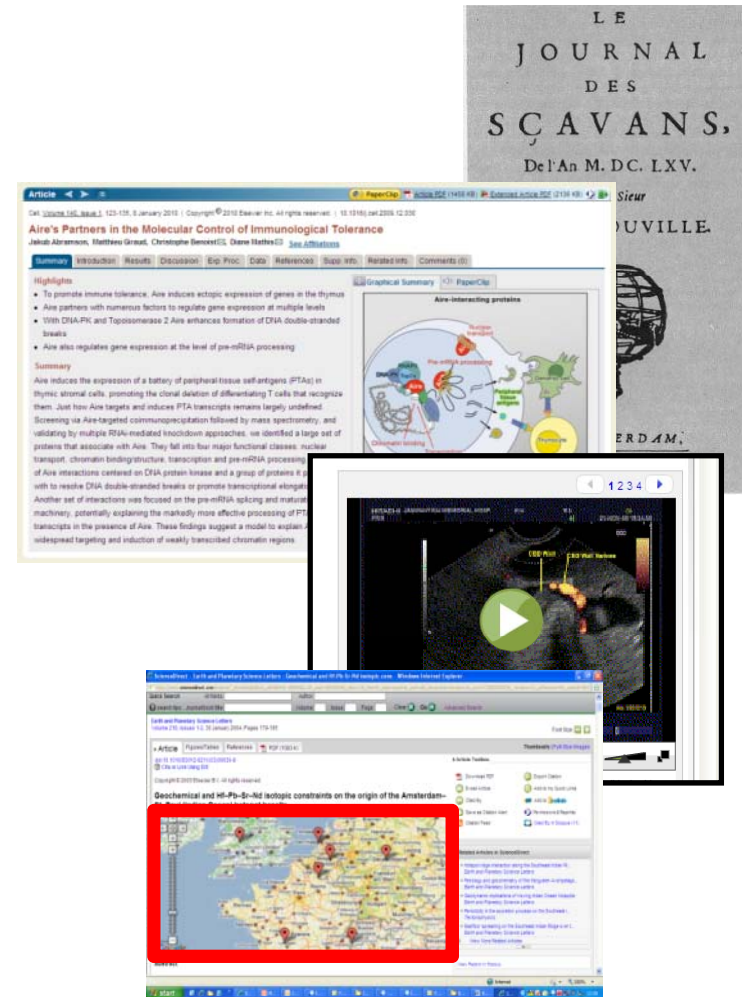
(A) Subcellular localization of M, Dyl, Tyn, and Zye proteins in epidermal cells of stage 15 wild-type embryos (A3 or A4 segment). Actin filaments were stained by phalloidin (red) and ZPD proteins with monospecific antibodies (green). Close-up views highlight the distinct localization of ZPD proteins along the extension.

(B) TEM analysis of M-HRP localization in stage 16 embryos. HRP activity leads to a dark stain revealing M-HRP accumulation within endocuticle layers of the denticle. Scale bar, 500 nm (see also Table S2).

(C) Codetection of Miniature (green) with either Dyl or Tyn (magenta); colocalization appears in white.

Content Innovation – A Journey

- Article of the Future
 - Why, How, What
 - Cell Press case
 - Feedback
 - Other disciplines
- Contextual Linking



Where are semantics, contextual linking?

Reflect: Elsevier Grand Challenge Winner

The image shows a screenshot of a web browser displaying a Cell journal article. The article title is "A Myristoyl Phosphotyrosine Switch Regulates c-Abl". The authors listed are Oliver Hantschel, Nagar, Sebastian Guettler, Jana Kretzschmar, Karel Dorey, John Kuriyan, and Purgas. The article is from the Cell journal, volume 121, issue 2, pages 287-298, published in 2004. The abstract discusses the mechanism of c-Abl kinase activation and inhibition by STI-571. Three green callout boxes with arrows point to specific parts of the page: "Identify Entities" points to the title and authors; "Link to Relevant DBs" points to a protein information window for Src; "Add Contextual Info" points to a chemical structure window for STI-571.

Cell

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LNA-based microRNA PCR system

Identify Entities

A Myristoyl Phosphotyrosine Switch Regulates c-Abl

Oliver Hantschel, Nagar, Sebastian Guettler, Jana Kretzschmar, Karel Dorey, John Kuriyan, Purgas

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Summary

The c-Abl tyrosine kinase is inhibited by mechanisms that are poorly understood. Disruption of these mechanisms in the Bcr-Abl oncoprotein leads to several forms of human leukemia. We found that like Src kinases, c-Abl 1b is activated by phosphotyrosine ligands. Ligand-activated c-Abl is particularly sensitive to the anti-cancer drug STI-571 / Gleevec (nilotinib) (STI-571). The SH2 domain-phosphorylated tail interaction in Src kinases is functionally replaced in c-Abl by an intramolecular engagement of the N-terminal myristoyl modification with the kinase domain. Functional studies coupled with structural analysis define a myristoyl/phosphotyrosine switch in c-Abl that regulates docking and accessibility of the SH2 domain. This mechanism offers an explanation for the observed cellular activation of c-Abl by tyrosine-phosphorylated proteins, the intracellular mobility of c-Abl, and it provides new insights into the mechanism of action of STI-571.

Link to Relevant DBs

Src

Protein

ENSMUSP0000029175 M. musculus

Rous sarcoma oncogene;

Domains, Sequence, Structure, Locus, Literature

MGSNKSKEP...RRRSLEPSNVHGAGCAFPASQTPSKPASADG

Add Contextual Info

STI-571

Chemical

Chemical structure of STI-571 (nilotinib) and a network diagram showing interactions between various proteins.

Use of Reflect: survey results

- Most useful terms were highlighted
 - Information provided was useful
 - Majority wants to see this continued
 - Less than 10% would never use it
 - Preference for Reflect to be switched on by default
 - Equal preference for in-text or as side-bar
 - Many suggestions for other entities to mark up
-
- Conclusion: we will bring this to ScienceDirect
 - And also investigate for other disciplines

Content Innovation – Summary

- Focus on discipline specificity
 - Different article presentations for different disciplines
 - Started with Life Sciences – extend to other disciplines
- Increase Interoperability
 - Allow for contextual linking applications
 - Collaborate with external databases
- Use external applications to add value
- Planning
 - Started in 2009 with basic functionality
 - Increases in 2010 with additional features
 - Further implementation in 2011 and later

Content Innovation – Questions?

Thank you!