WILEY

Preservation e Post-cancellation Access

CAPES
26/03/2015

200 Anos de Excelência

A Wiley tem sido uma valiosa parceira em educação e pesquisa há mais de 200 aos. Os produtos e serviços da Wiley ajudam educadores, estudantes, pesquisadores e profisionais ao redor ro Mundo a alcançar seus objetivos e realizar suas aspirações.

5,000 Colaboradores

$1.8 Bilhões Faturamento

50% do Faturamento fora dos EUA

50% do Faturamento é Digital

WILEY

A maior editora de Sociedades do Mundo

WILEY

Wiley: Conteúdo de Qualidade

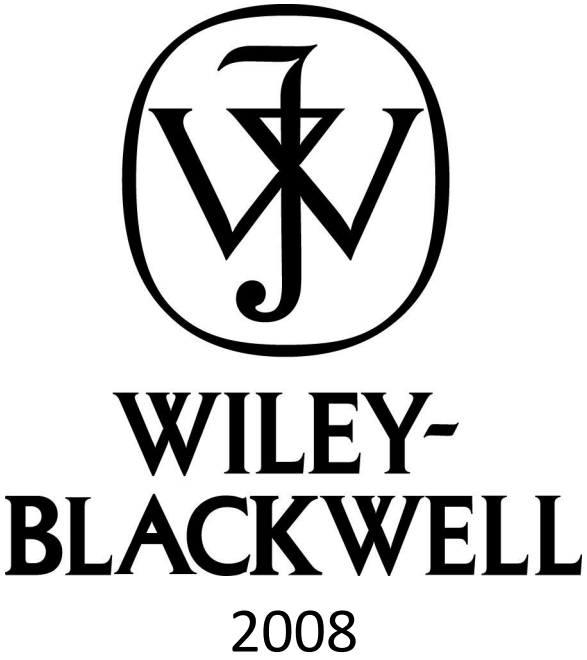
WILEY

WILEY ONLINE LIBRARY

O QUE PUBLICAMOS?

- +1.500 periódicos = +4 milhões de artigos!
- +15.000 livros online
- 160 Obras de referência (Reference Works)
- 17 Current Protocols (Laboratory Manuals featuring over 10,000 protocols)
- 946 Arquivos de periódicos (journals publicados antes de 1997)

2008 - FUSÃO WILEY + BLACKWELL



= WILEY

Instituições com acesso completo

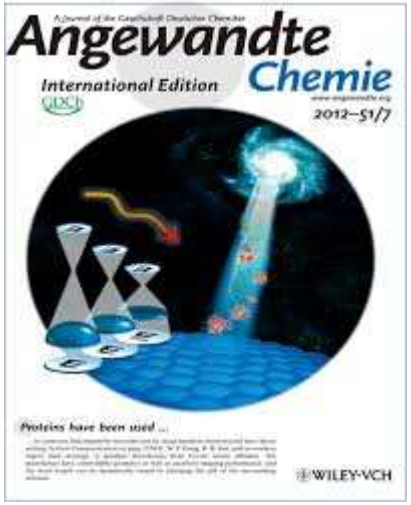
Periódicos e Backfiles

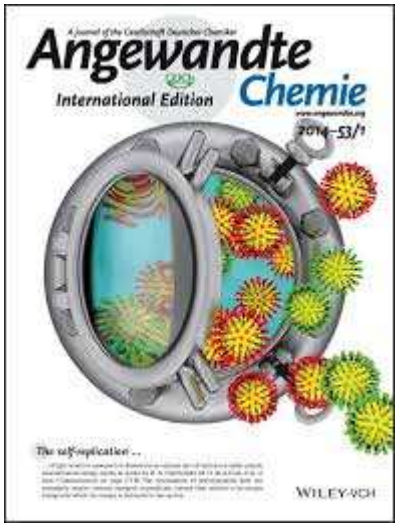
WILEY

Acesso via Portal CAPES

- **1.333 periódicos**
- 3 milhões+ artigos
- Conteúdo desde 1997
- 750 sociedades
- Accesso 24/7
- **178 periódicos ainda não são assinados!**

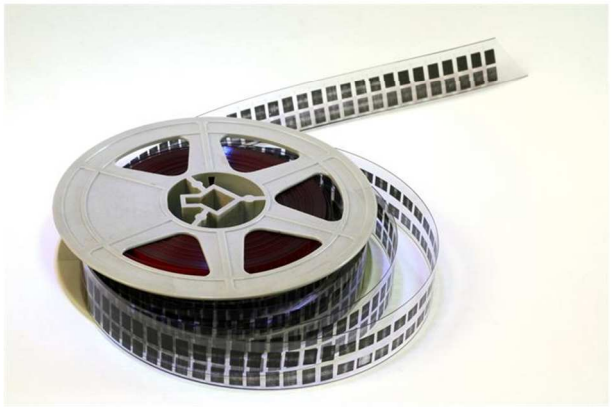
Como era no passado…



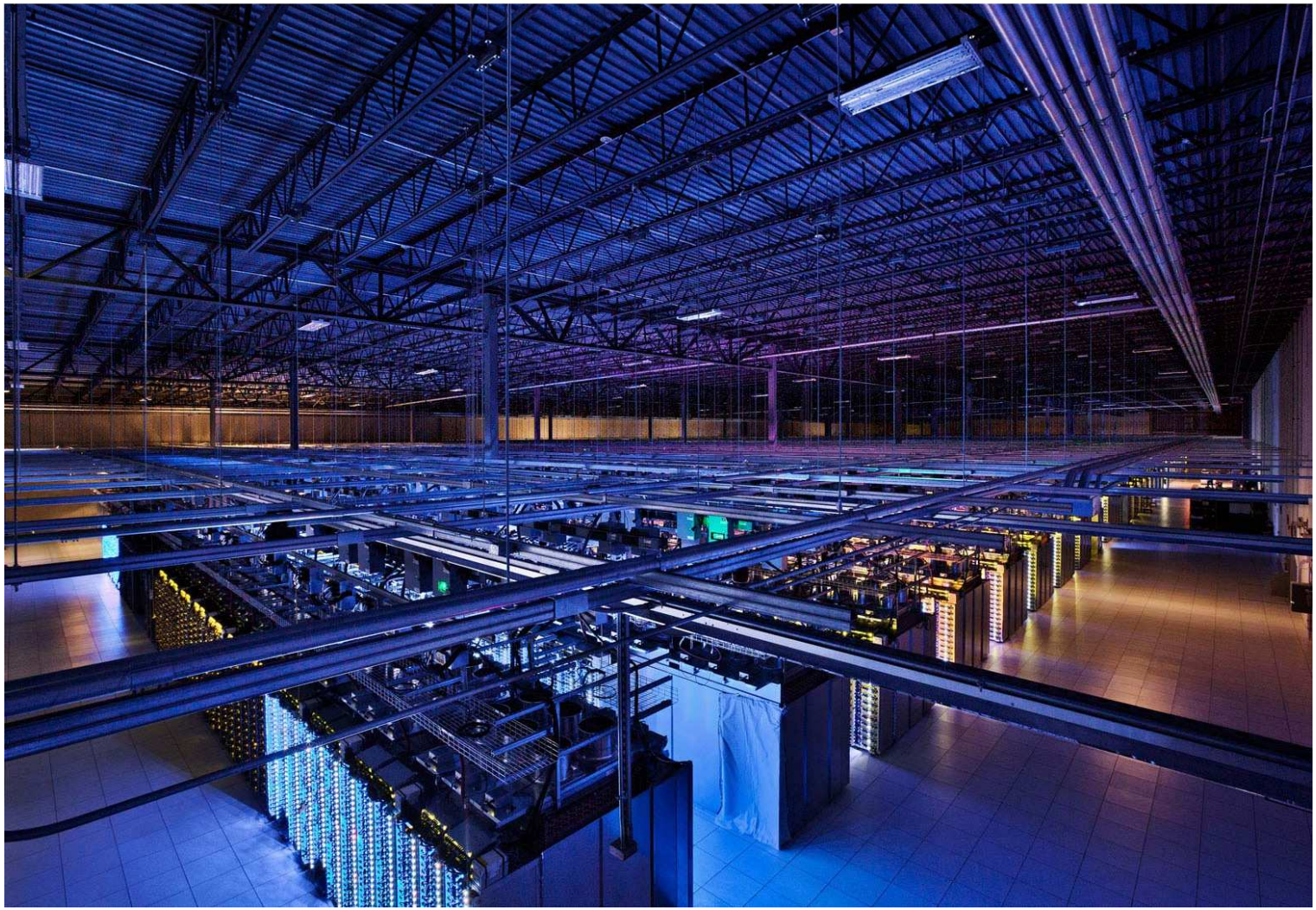


Como era no passado…

Como era no passado…



Como é agora



Porque a Preservação é tão importante ?

Preservação…

…é um componente essencial do ciclo de pesquisas Científica.

… garante a continuidade de acesso

—Preservação Digital

—Acesso pós-cancelamento

… é uma questão de confiança

—Precisa de uma colaboração estreita entre editoras, bibliotecas e arquivadores.

… responde a demanda dos consumidores e necessidades de mercado.

Desafios da Preservação

- Não há um padrão nos formatos dos conteúdos ou processos.
  - Grandes editoras de STM <> the “long tail”
  - Que arquivos precisam ser preservados ?
- Diferenças em direitos de acesso.
  - Conteúdos assinados <> Acesso a Coleções.
  - Conteúdo Open Access
  - O que acontece com material que é OA ?
- Artigos estáticos <> Conteúdo Dinâmico
  - Implicações para Preservação ?

Estudo de Caso – O que estamos realmente preservando ?

O Conteúdo Digital não mais “espelha” o impresso.

- —Pode conter “enriched data”
- —Liks para arquivos
  - —Dados de pesquisa
  - —Materiais complementares.
- —Camada de apresentação Dinâmica
  - —Ex.: Wiley’s ‘Anywhere Article’
- —Arquivos fonte e arquivos de apresentação não são a mesma coisa.

Estudo de Caso – O que estamos realmente preservando ?

Proteomics 2013, 13, 37–47 DOI 10.1002/pmic.201200233 37

RESEARCH ARTICLE

Quantitative proteomic analysis to decipher the differential apoptotic response of bortezomib-treated APL cells before and after retinoic acid differentiation reveals involvement of protein toxicity mechanisms

Sandrine Uttenweiler-Joseph[1,2], David Bouyssié[1,2], David Calligaris[1,2], Pierre G. Lutz[1,2], Bernard Monsarrat[1,2] and Odile Burlet-Schiltz[1,2]***

[1] CNRS, IPBS (Institut de Pharmacologie et de Biologie Structurale), Toulouse, France
[2] Université de Toulouse, UPS, IPBS, Toulouse, France

Received: June 11, 2012
Revised: August 30, 2012
Accepted: October 2, 2012

The ubiquitin-proteasome system allows the targeted degradation of proteins and plays a critical role in the regulation of many cellular processes. Proteasome inhibition is a recent antitumor therapeutic strategy and bortezomib was the first proteasome inhibitor approved for clinical use. In this study, we used the NB4 cell line to investigate the effects of bortezomib toward acute promyelocytic leukemia cells before and after retinoic acid-induced differentiation. We showed that apoptosis level after bortezomib treatment is higher in NB4 cells than in differentiated NB4 cells. To compare early protein variations upon bortezomib treatment in both NB4 cell populations, we performed a quantitative proteomic analysis based on iTRAQ peptide labeling followed by data analysis with in-house developed scripts. This strategy revealed the regulation of 14 proteins principally involved in protein stress response and apoptosis in NB4 cells after proteasome inhibition. Altogether, our results suggest that the differential level of apoptosis induced by bortezomib treatment in both NB4 cell populations could result from distinct protein toxicity level.

Keywords:
Cell biology / iTRAQ / Kinetic of protein variation / Proteasome inhibition

Additional supporting information may be found in the online version of this article at the publisher's web-site

1 Introduction

The ubiquitin-proteasome system (UPS) allows targeted protein degradation and represents an essential cellular process that contributes to the regulation of many cellular mechanisms including cell cycle progression, signal transduction, stress response, apoptosis and protein quality control. A dysfunction of this system can lead to several pathologies like inflammation disorders, neurological diseases, and cancers.

Correspondence: Dr. Sandrine Uttenweiler-Joseph, IPBS, 205 route de Narbonne, BP64182, F-31077 Toulouse Cedex, France
E-mail: Sandrine.Uttenweiler@ipbs.fr
Fax: +33 5 61 17 59 94

Abbreviations: AML, acute myeloid leukemia; **APL**, acute promyelocytic leukemia; **BZ**, bortezomib; **FDR**, false discovery rate; **MM**, multiple myeloma; **mRNP**, messenger ribonucleoprotein; **NB4 + RA**, RA-differentiated NB4 cells; **PARP**, poly(ADP-ribose) polymerase; **RA**, retinoic acid; **SCX**, strong cation exchange; **SG**, stress granules; **SR**, stress response; **UPR**, unfolded protein response; **UPS**, ubiquitin-proteasome system

*Current address: Dr. David Calligaris, Mass Spectrometry Laboratory, GIGA-Research, University of Liege, 4000 Liege, Belgium.
**Additional corresponding author: Dr. Odile Burlet-Schiltz, E-mail: Odile.Schiltz@ipbs.fr

The UPS also represents a pharmacological target in cancer therapy as illustrated by the use of proteasome inhibitors to treat several malignancies [1]. Bortezomib (Velcade®, formerly PS-341) was the first proteasome inhibitor approved by the FDA for the treatment of multiple myeloma (MM) and relapsed mantle cell lymphoma [2, 3]. This agent and more recent proteasome inhibitors like carfilzomib or NPI-0052 are currently being evaluated in combination with other agents in patients with solid tumors [4, 5].

Proteasome inhibitors have antiproliferative or proapoptotic activity against cancer cells through multiple mechanisms like stabilization of cell-cycle regulators and proapoptotic factors, induction of ER stress, activation of the unfolded protein response (UPR), inhibition of the nuclear factor kappa B inflammatory pathway, and increased generation of reactive oxygen species [6]. The in vitro and in vivo effects of proteasome inhibitors are tumor-dependent explaining the different therapeutic efficacy of these drugs. Many studies where performed to decipher these mechanisms but most of them where targeted on specific pathways and only few global transcriptomic and/or proteomic analyses were performed to discover new and unexpected modes of action [7–9] or to explain the sensitivity variation to proteasome inhibition of different cell lines from a same cancer [10].

Another important feature of proteasome inhibitors is their selectivity for tumor cells in patients. For example, MM cell lines are up to 40 times more sensitive to the proapoptotic effects of bortezomib (BZ) than are peripheral blood mononuclear cells from healthy individuals [11]. The exact mechanisms explaining this selectivity are not yet known but several hypotheses were already proposed based on the general idea that proteasome inhibitor sensitivity is linked to proliferation and/or deregulated cell cycle progression [6, 12].

In the present study, we aimed to give new insights into the differential effects of BZ toward malignant and mature hematopoietic cells from the same lineage. The NB4 cell line was used as a model because these acute promyelocytic leukemia (APL) cells are able to differentiate along the granulocytic pathway when exposed to retinoic acid (RA) leading to phenotypically mature neutrophil granulocytes [13, 14]. The level of apoptosis measured after BZ treatment proved that NB4 cells are more sensitive to proteasome inhibition than the RA-differentiated NB4 (NB4 + RA) cells. A quantitative proteomic analysis using iTRAQ technology was set up to compare the protein variations upon BZ treatment in NB4 and NB4 + RA cells. To decipher the early events leading to the apoptotic cascade initiation, the protein variations were followed at several time points thanks to the multiplex iTRAQ reagents that are ideally suited for time course studies. Based on our past experience with the development of the MFPaQ software to extract quantitative data from isotopic labeling experiments using either ICAT or SILAC methods [15], in-house scripts were elaborated to analyze the iTRAQ quantitative data. The results obtained suggest that NB4 cells are more affected by protein toxicity than NB4 + RA cells after BZ treatment.

2 Materials and methods

2.1 Cell culture and differentiation

Promyelocytic NB4 cells [13] were cultured in RPMI 1640 medium (Invitrogen) with 10% fetal bovine serum (PAA Laboratories), 2 mM glutamine and 1% penicillin-streptomycin (Invitrogen). Cells were grown in a humidified atmosphere at 37°C and 5% CO_2. Cell viability was assessed by standard trypan blue dye exclusion assay. Exponentially growing NB4 cells were seeded at 2×10^5 cells/mL 16 h prior all-*trans* RA treatment (Sigma-Aldrich, St Louis, MO; final concentration of 10^{-6} M). Differentiation was assessed by the percentage of nitro blue tetrazolium (Sigma)-positive cells.

2.2 Apoptosis analysis by flow cytometry

NB4 cells in logarithmic-phase growth or after different days of RA-induced differentiation were treated or not (control) with 0.1 nM to 1 μM BZ for up to 48 h. BZ (Velcade®) was generously provided by Millennium Pharmaceuticals Inc. (Cambridge, MA, USA). Apoptotic cells were assessed using the Annexin V-FITC/propidium iodide detection kit supplied by BD PharmingenTM (San Jose, CA, USA) as described previously [16].

2.3 Cell lysates, in-solution digestion, and iTRAQ labeling

Duplicate samples (a and b) of NB4 cells in logarithmic-phase growth or after 3 days of RA-induced differentiation (NB4 + RA) were treated or not (control) with 10 nM BZ. Cells were harvested by centrifugation before (0 h) and 6, 12, and 24 h after treatment. Cells were washed three times with ice cold PBS, frozen in liquid nitrogen, and stored at −80°C until further use. The harvested cells were resuspended in lysis buffer (10 mM HEPES, pH 7.5, 10 mM KCl, 1 mM $MgCl_2$) containing protease inhibitors (Roche, Indianapolis, Indiana, USA). Crude cell extracts were centrifuged for 10 min at 800 × *g* and the resulting supernatants were centrifuged at 100 000 × *g* for 1 h. The latter supernatants correspond to the cytosolic extracts and protein concentration was determined using the BioRad Protein Assay (BioRad, Hercules, CA, USA). A total of 100 μg of protein per each time point was used for iTRAQ labeling. Triethylammonium bicarbonate and n-dodecyl β-D-maltopyranoside were added to each sample to reach a final concentration of 0.5 M and 0.01%, respectively. Proteins were then reduced and alkylated according to the iTRAQ kit manufacturer's instruction (Applied Biosystems). Samples were digested with trypsin (Sequence grade Modified, Promega, Madison, WI, USA) using 1:50 ratio at 37°C overnight. Labeling with the iTRAQ reagents was performed according to manufacturer's instructions and as detailed in Supporting Information Table 1. After isobaric

WILEY

Estudo de Caso – O que estamos realmente preservando ?

<?xml version="1.0" encoding="US-ASCII" standalone="no"?>
<!DOCTYPE WileyML3G [<!ENTITY % wileyml3g.ent SYSTEM
"http://vendors.wiley.com/dtds/wileyml3g/wiley.ent">
%wileyml3g.ent;]> <component version="2.0"
xmlns="http://www.wiley.com/namespaces/wiley"
xmlns:wiley="http://www.wiley.com/namespaces/wiley/wiley"
type="serialArticle" xml:lang="en" xml:id="rcm4"> <header>
<publicationMeta level="product"> <doi origin="wiley"
registered="yes">10.1002/(ISSN)1097-0231</doi> <issn
type="print">0951-4198</issn> <issn type="electronic">1097-
0231</issn> <idGroup> <id type="product" value="RCM"/>
</idGroup> <titleGroup> <title type="main" sort="RAPID
COMMUNICATIONS IN MASS SPECTROMETRY">Rapid
Communications in Mass Spectrometry</title> <title
type="short">Rapid Commun. Mass Spectrom.</title>
</titleGroup> </publicationMeta>

Estudo de Caso – O que estamos realmente preservando ?

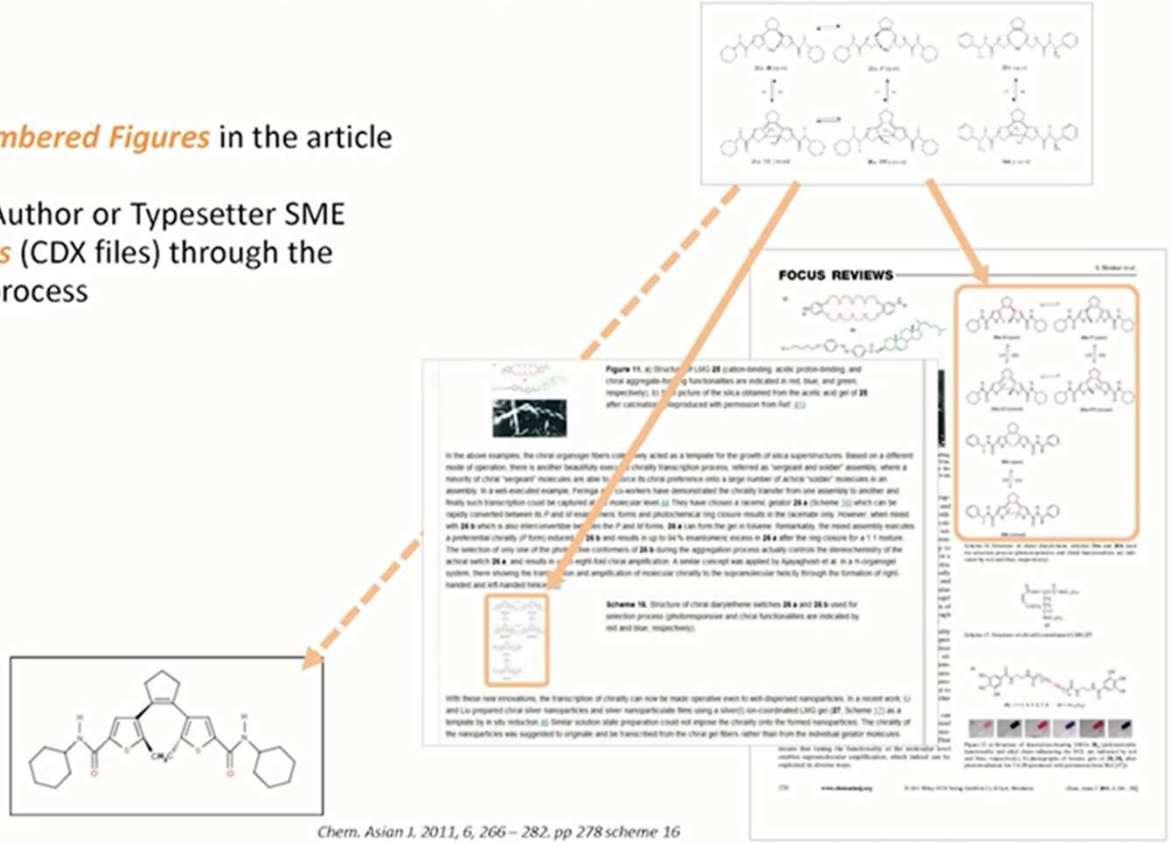
WILEY

Estudo de Caso – O que estamos realmente preservando ?

Primary Structures
(Featured Compounds)

Defined as ***Numbered Figures*** in the article

Derived from Author or Typesetter SME drawn ***schemes*** (CDX files) through the Enumeration process



Chem. Asian J. 2011, 6, 266 – 282. pp 278 scheme 16

Wiley – Parceiros de Preservação

PORTICO

Your content.
Preserved here.

Política de “pós-cancelamento” da Wiley

- Títulos assinados
  - Acesso perpétuo desde 1997.
  - CAPES

- Acesso a Coleções
  - Acesso perpétuo aos anos assinados.

Cenário #1

- Biblioteca cancela assinatura de um Journal
  - Acesso “pós-cancelamento” desde 1997.
  - Conteúdo arquivado no Portico e CLOCKSS.
    - Pode ser acessado se “trigger event” acontecer.

Cenário #2

- Biblioteca cancela acesso a Coleção (‘big deal’)
  - Acesso pós-cancelamento para os anos assinados.
  - Conteúdo arquivado em Portico e CLOCKSS
    - Poderá ser acessado no caso de um “trigger event” acontecer.

Cenário #3

—Conteúdo não está mais disponível através da Editora.

Trigger events:

—Encerramento das atividades da Editora.
—Cancelamento de um título pela Editora.
—Edições anteriores não são mais oferecidas pela Editora.
—Falha geral e/ou “catastrófica” na plataforma da Editora.

Caso Real – ‘trigger event’ da Wiley

- A auditoria do Portico no conteúdo da Wiley identificou que 2 títulos não estavam mais disponíveis através de sua plataforma.
  - Applied Geographic Studies (8 edições)
  - P2: Pollution Prevention Review (9 edições)
- Portico ofereceu-se para abrir o acesso aos arquivos dos 2 títulos.
- Os títulos haviam sido cancelados/foram fundidos e não estavam mais disponíveis na Wiley Online Library
- Wiley decidiu que preferia hospedar este conteúdo em sua plataforma, ao invés de disparar o acesso através do Portico.
- Portico forneceu os arquivos para a Wiley fazer o upload na Wiley Online Library

O futuro…

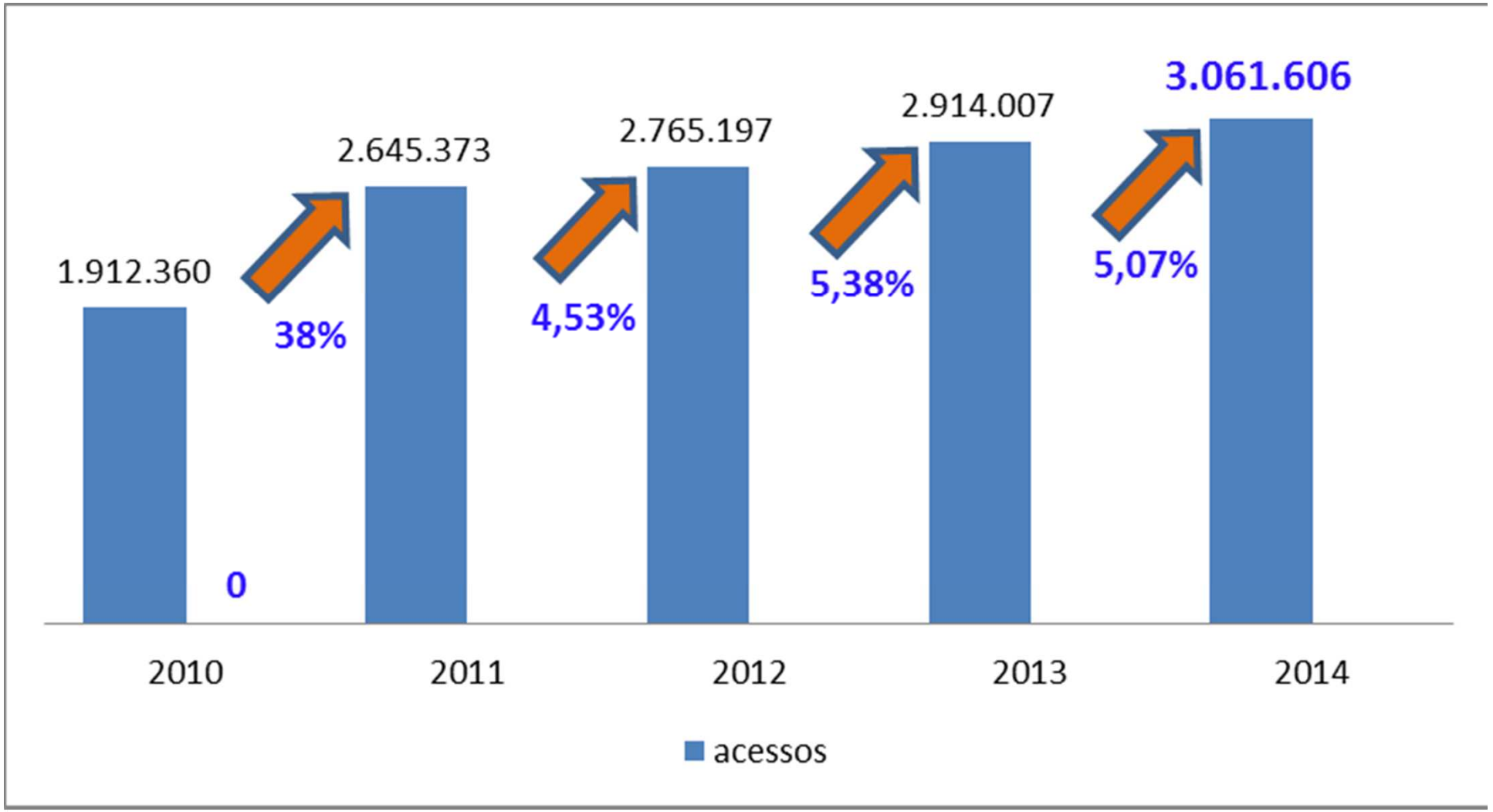
—A Wiley continuará a garantir que seus produtos, serviços e políticas atendam as necessidades dos Clientes e demandas do mercado.

—A Wiley continuará a dialogar com todos os seus “stakeholders” para garantir que tenha sempre soluções confiáveis e robustas disponíveis para oferecer acesso e preservação no longo prazo.

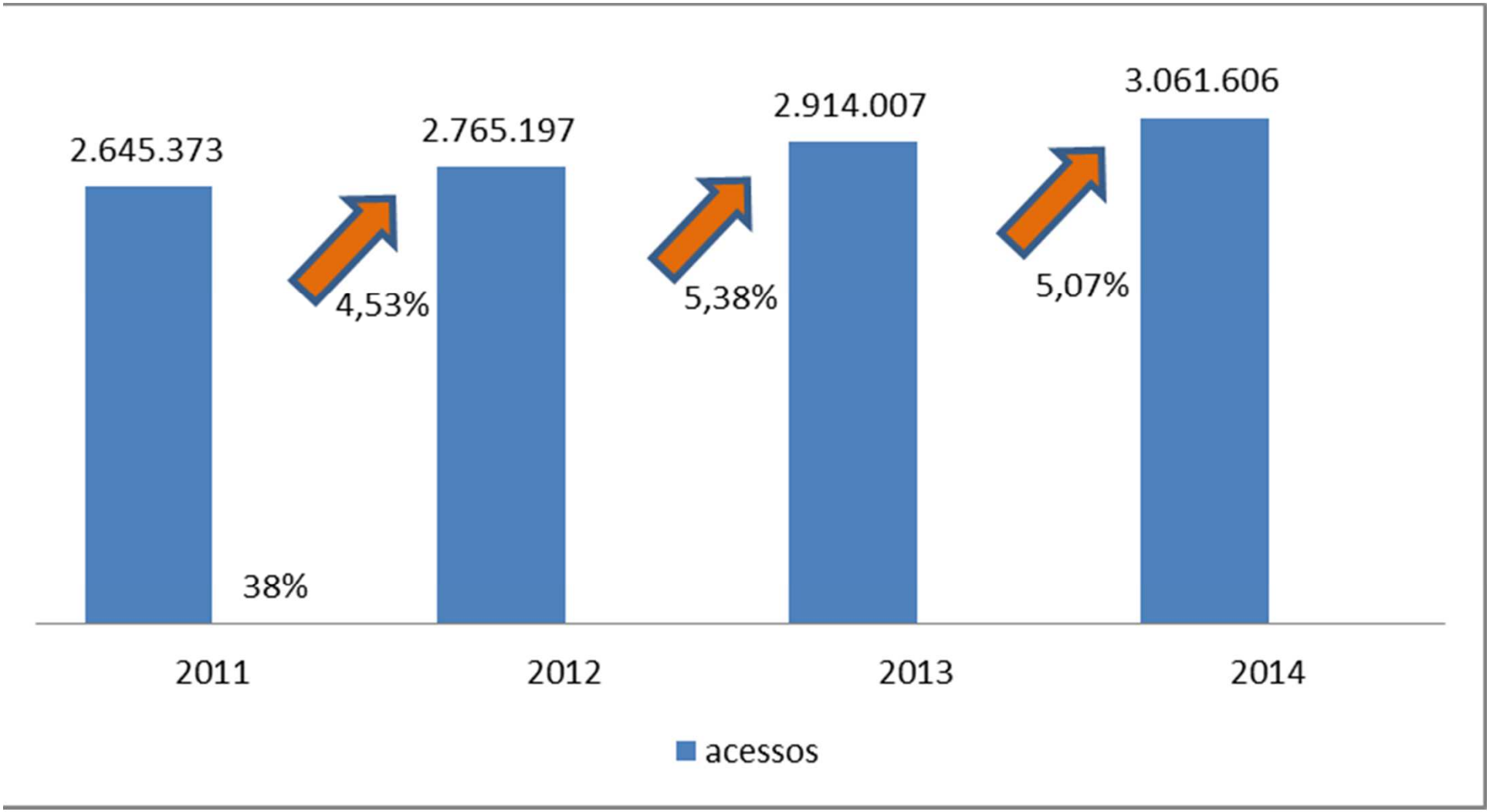
—A Wiley irá desenvolver estratégias de preservação que levem em conta a crescente complexidade dos conteúdos e produtos digitais.

- Appendix

Estatística periódicos



Estatística periódicos



WILEY

Repositórios backup

- TODOS os periódicos WILEY tem acesso via Portico e CLOCKSS.
- Todos os livros online da Wiley Online Library estão incluidos no Portico.
- WILEY foi uma das fundadoras do Portico.

  WILEY faz parte do conselho de administração do Portico e

  é membro do conselho do CLOCKSS.
- Wiley arca com aproximadamento $150,000 ao ano para manutenção dos 2 repositórios.
- Ambas são organizações de qualidade com processos e tecnologias robustas, e financieiramente sustentáveis.

Wiley e Portico

- Os periódicos WILEY foram adicionados ao Portico desde a sua fundação.
- Os livros online da WILEY foram adicionados em 2010
- O conteúdo completo da plataforma Wiley Online Library está disponível via Portico
- Novos conteúdos são adicionados ao Portico imediatamente após a publicação.
- O processo de inclusão de novos conteúdos da WILEY no repositório Portico é automático.

Repositórios backup

- WILEY confia que Portico e CLOCKSS possuem uma cobertura adequada, garantindo a longo prazo a preservação do conteúdo STMS publicado pela WILEY
- Os 2 repositórios possuem mecanismos similares "trigger mechanisms".
- Até hoje nenhum cliente Wiley necessitou solicitar cobertura do Portico ou do CLOCKSS!
- A Wiley mantém todos os artigos publicados em sua plataforma, mesmo dos periódicos que foram descontinuados ou transferidos para outras editoras.
- Caso 1990: Neste ano a WILEY inadvertidamente removeu 2 periódicos de sua plataforma online. Após algumas avaliações, a WILEY reintegrou o conteúdo à sua plataforma (WOL) e desde então adotou como política manter todos os conteúdos em sua plataforma online, wileyonlinelibrary.com

CLOCKSS

CLOCKSS está em negociações finais com a RNP (*Rede Nacional de Ensino e Pesquisa - RNP*) para inclusão de uma ramificação CLOCKSS no Brasil.