



Publishing platforms as metadata hubs

NISO Metadata in a Digital Age Forum
Phoenix, June 4, 2008

Kevin Cohn
Director of Client Services

About me

- Statistician - Carnegie Mellon University
- Publisher - Mary Ann Liebert, Inc.
- Vendor - Atypon Systems, Inc.

About Atypou

- Publisher services company based in Santa Clara (Silicon Valley), California
- Current clients include JSTOR, Blackwell Synergy, and University of Chicago Press
- Technology partner for CrossRef's citation linking resolution system
- New clients include *N Engl J Med*, American Chemical Society, BioOne, and more

This talk is about...

- Providers (producers) of metadata: who they are and how they provide it
- Consumers of metadata: who they are and how and when they consume it
- How publishing platforms deliver metadata from the providers to the consumers

Things to keep in mind

- Incoming/outgoing formats
 - NLM, Dublin Core, RSS, etc.
 - Transformations are needed
- Exchange mechanisms
 - FTP, Z39.50, email, etc.
 - Push vs. pull

Providers

- Authors
- Publishers
- Librarians
- Secondary publishers
- End-users

There is an increasing number of providers and consumers of content metadata. This, coupled with the use of different DTDs and exchange protocols, demands that publishers' platforms serve as advanced metadata hubs. In this presentation, the speaker will discuss his experience with **Atypon's publishing platform serving as a metadata hub.**

Publishers

- Produce the majority of metadata that is consumed within our industry
- Uploaded in submission packages to our platform via WebDAV (FTP on steroids)
- Metadata provided as XML or SGML (the latter to support late adopters of XML)
- NLM is the house DTD at Atypon, and is quickly becoming the “standard,” but...

NLM DTD

- Did you know there are three different versions of it?
 - Archiving, Publishing, and Book
- Plus plenty of variations that are “NLM-based” or “informed by” one of the above
- Not a standard (yet), but there is certainly a growing path dependence (LoC, BL...)

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So many input formats

- NLM Journal Archiving and Interchange DTD (v1.0 and v2.2) and Book DTD (v2.3)
- ScholarOne XML DTD
- Five proprietary XML DTDs
- Two proprietary SGML DTDs
- ONIX
- Dublin Core

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- Abstract

A Cytomegalovirus Vaccine for Transplantation: Are We Closer?

Vera Go and Richard B. Pollard

University of California, Davis, Health System, Sacramento

(See the article by Wloch et al., on pages 1634–42.)

Cytomegalovirus (CMV), a betaherpesvirus, causes significant human morbidity and mortality. It is present in at least 60% of the US population [1], with a prevalence of >90% in high-risk groups, including men who have sex with men [2, 3]. In immunocompetent hosts, CMV infection is usually asymptomatic, but it persists throughout an individual's lifetime and has the potential to reactivate and cause disease. CMV also causes significant disease in newborns, which can result in sensorineural hearing loss, other central nervous system abnormalities, and death. In immunocompromised individuals, CMV is the most common viral cause of severe disease, including gastrointestinal manifestations and pneumonia in the transplant population and, in addition, retinitis in HIV-positive individuals [4, 5].

Current management of CMV disease uses antivirals that may have significant hematopoietic and renal toxicities along with sometimes-adverse drug-drug interactions. Thus, an effective CMV vaccine would be beneficial in decreasing the need for anti-CMV drugs. In 2001, the Institute of Medicine reported that the development of a CMV vaccine is of the highest priority in the 21st century [6]. Vaccine strategies have targeted CMV structural proteins, including the major surface glycoprotein B (gB) and tegument phosphoprotein 65 (pp65), because they have been shown to induce the dominant antibody and cellular immune responses, respectively [7–9]. CMV nonstructural proteins that elicit a strong humoral response, such as immediate-early 1 (IE1), have also been used. Several CMV vaccines have been studied, with mixed results [10]. Initial animal studies have been performed using an alphavirus-like replicon particle that expresses various combinations of pp65, IE1, and gB, with promising results [11]. Studies with live attenuated human Towne strain CMV vaccine have been disappointing in that the vaccine has not prevented CMV infection in seronegative individuals [12–15]. A phase 1 study of live recombinant human CMV Towne/Toledo chimeric vaccines in CMV-seropositive subjects produced no significant cellular or humoral immune response to the vaccine [16]. A recombinant gB protein with MF59 adjuvant (gB/MF59) vac-

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Since immunocompromised individuals such as transplant recipients are a target population for CMV vaccination, it would be of benefit to use a virus-free vaccine [20]. DNA vaccines have been shown to induce significant T cell (both CD4⁺ and CD8⁺) and antibody responses [21] and, theoretically, for prolonged periods [22]. Alone, they are poorly immunogenic, but they can be combined with an adjuvant or modified to increase their immunogenic potential. They usually require large quantities of antigen to obtain a sufficient response, but they are relatively easy to produce.

In this issue of the *Journal*, Wloch et al. [23] present the results of a phase 1 clinical trial of a bivalent DNA CMV vaccine, VCL-CB01 [24], containing plasmids encoding for gB and pp65 along with poloxamer CRL1005 and benzalkonium chloride to increase immunogenicity. The trial was an open-label, dose-escalating study of 44 adults who were either seronegative or seropositive for CMV. Wloch et al. evaluated 2 doses, 1 and 5 mg, in a

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3-dose schedule, with vaccine administered at weeks 0, 2, and 8. In addition, a group was evaluated using an accelerated 5-mg-dose schedule, with vaccine administered on days 0, 3, 7, and 28. The primary objectives of the study were to assess the safety profile and immunogenicity of the vaccine.

The authors found VCL-CB01 to be well tolerated, with pain at the site of injection to be the most common adverse event (AE). Of the Towne CMV vaccine, 81.8% developed a grade 1 AE, and 40.9% developed a grade 2 AE that resolved after several days. The AEs observed were not associated with dose or schedule. These results are comparable to those observed with other phase 1 trials of adult human CMV vaccines.

Immunogenicity was evaluated by assessing antibody and T cell responses to gB and pp65, respectively, at various time points up to week 32 after the initial vaccination. Using standard ELISA methods, a positive gB antibody response was defined as >2.5 times that of pooled CMV-seronegative serum specimens. In those individuals who developed antibody against gB, the measured serum anti-gB response was comparable to that observed in other CMV vaccine studies. Interestingly, no CMV-seropositive individual developed appreciable anti-gB antibody, and a small fraction of the CMV-seronegative individuals developed an anti-gB antibody response. Antibody levels peaked around weeks 12–16 after vaccination. It will be of interest to determine why CMV-seropositive individuals do not seem to mount a humoral response when reexposed to gB antigen and whether this response can be induced via additional vaccine doses or through a prime-boost strategy with other CMV vaccines.

T cell responses to VCL-CB01 were evaluated by pp65 ex vivo interferon (IFN)- γ enzyme-linked immunospot (ELISPOT) assays. They were considered to be positive if >50 $\text{sfu}/1 \times 10^6$ peripheral blood mononuclear cells were present or there was a >2-fold increase in spot-forming units relative to that seen in controls. T

cell responses were measured at several time points up to 16 weeks after vaccination. In CMV-seropositive individuals, 12.9%–37.9% had a T cell response to pp65, compared with 25.0%–50.0% of CMV-seronegative individuals; responses peaked at weeks 10–12 after vaccination. This response, too, is modest, faring better than the live recombinant CMV Towne/Toledo chimeric vaccines that failed to induce T cell responses [16] but not as well as the Towne CMV vaccine that showed a 45%–69% IFN- γ CD8⁺ T cell response with or without recombinant human interleukin-12 [25].

The highlight of Wloch et al.'s study is the use of the cultured IFN- γ ELISPOT assay to evaluate whether VCL-CB01 primed the T cell memory response at week 32, or 24 weeks after vaccination. The authors found a positive response to pp65 in 63.6% (14/22) and to gB in 59.1% (13/22) of CMV-seronegative participants, with 68.2% subjects (15/22) overall responding to either antigen. This strongly suggests that VCL-CB01 has the ability to prime T cells, such that, on rechallenge with antigen, antigen-specific T cells can proliferate and secrete IFN- γ . Moreover, a persistent response was observed when tested at weeks 16 and 32 in those subjects who received the 5-mg dose.

In all, the VCL-CB01 vaccine at the 5-mg dose with a 3-dose schedule at weeks 0, 2, and 8 holds promise, because it elicits appropriate immunologic responses with typical AEs in CMV-seronegative individuals. Additional studies evaluating its effectiveness in preventing CMV infection and disease and the duration of immunity should be pursued. A limitation of current CMV vaccines being studied is the lack of immune response to vaccine in seropositive individuals. CMV disease in transplant recipients may result from primary infection or reactivation. Moreover, there is an increased risk of developing disease in those who are CMV-seropositive [26]. Seropositivity has been associated with stable levels of CMV-specific CD4⁺ T cells, suggesting an appropriate humoral and cellular response to CMV infection in long-term renal transplant recipients [27]. Interestingly, the

CMV vaccines studied to date, including VCL-CB01, have shown no to minimal immunologic responses in CMV-seropositive individuals. Further studies attempting to increase immunogenicity or identify other CMV antigens associated with disease in seropositive individuals would be beneficial.

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A Cytomegalovirus Vaccine for Transplantation: Are We Closer?

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(See the article by Wloch et al. on pages 1634–1642.)

Cytomegalovirus (CMV), a betaherpesvirus, causes significant human morbidity and mortality. It is present in at least 60% of the US population [1], with a prevalence of >90% in high-risk groups, including men who have sex with men [2, 3]. In immunocompetent hosts, CMV infection is usually asymptomatic, but it persists throughout an individual's lifetime and has the potential to reactivate and cause disease. CMV also causes significant disease in newborns, which can result in sensorineural hearing loss, other central nervous system abnormalities, and death. In immunocompromised individuals, CMV is the most common viral cause of severe disease, including gastrointestinal manifestations and pneumonia in the transplant population and, in addition, retinitis in HIV-positive individuals [4, 5].

Current management of CMV disease uses antivirals that may have significant hematopoietic and renal toxicities along with sometimes-adverse drug-drug interactions. Thus, an effective CMV vaccine would be beneficial in decreasing the need for anti-CMV drugs. In 2001, the Institute of Medicine reported that the development of a CMV vaccine is of the highest priority in the 21st century [6]. Vaccine strategies have targeted CMV structural proteins, including the major surface glycoprotein 65 (gp65) and tegument phosphoprotein 65 (pp65), because they have been shown to induce the dominant antibody and cellular immune responses, respectively [7–9]. CMV nonstructural proteins that elicit a strong humoral response, such as immediate-early 1 (IE1), have also been studied. Several CMV vaccines have been used, with mixed results [10]. Initial animal studies have been performed using an alphavirus-like replicon particle

that expresses various combinations of pp65, IE1, and gp, with promising results [11]. Studies with live attenuated human Towne-strain CMV vaccine have been disappointing in that the vaccine has not prevented CMV infection in seronegative individuals [12–15]. A phase 1 study of live recombinant human CMV Towne/Toledo chimeric vaccines in CMV-seropositive subjects produced no significant cellular or humoral immune response to the vaccine [16]. A recombinant gp protein with MF59 adjuvant (gpIMF59) vac-

ine induced high levels of IgG antibodies to gp in healthy adults who were given 2 priming doses followed by a booster dose at 6 months [17]. A canarypox-CMV recombinant gp vaccine, ALVAC-CMV(gp), could not elicit a significant neutralizing antibody response [18], nor did it show benefit in a prime-boost strategy or in a simultaneous vaccine strategy with the gpIMF59 vaccine [19].

Since immunocompromised individuals such as transplant recipients are a target population for CMV vaccination, it would be of benefit to use a virus-free vaccine [20]. DNA vaccines have been shown to induce significant T cell (both CD4⁺ and CD8⁺) and antibody responses [21] and, theoretically, for prolonged periods [22]. Alone, they are poorly immunogenic, but they can be combined with an adjuvant or modified to increase their immunogenic potential. They usually require large quantities of antigen to obtain a sufficient response, but they are relatively easy to produce.

In this issue of the *Journal*, Wloch et al. [23] present the results of a phase 1 clinical trial of a bivalent DNA CMV vaccine, VCL-CB01 [24], containing plasmids encoding for gp and pp65 along with polyoxamer CRL1005 and benzalkonium chloride to increase immunogenicity. The trial was an open-label, dose-escalating study of 44 adults who were either seronegative or seropositive for CMV. Wloch et al. evaluated 2 doses, 1 and 5 mg, in a

3-dose schedule, with vaccine administered at weeks 0, 2, and 8. In addition, a group was evaluated using an accelerated 5-mg-dose schedule, with vaccine administered on days 0, 3, 7, and 28. The primary objectives of the study were to assess the safety profile and immunogenicity of the vaccine.

The authors found VCL-CB01 to be well tolerated, with pain at the site of injection to be the most common adverse event (AE). Of the study participants, 81.8% developed a grade 1 AE, and 40.9% developed a grade 2 AE that resolved after several days. The AEs observed were not associated with dose or schedule. These results are comparable to those observed with other phase 1 trials of adult human CMV vaccines.

Immunogenicity was evaluated by assessing antibody and T cell responses to gp and pp65, respectively, at various time points up to week 32 after the initial vaccination. Using standard ELISA methods, a positive gp antibody response was defined as >2.5 times that of pooled CMV-seronegative serum specimens. In those individuals who developed antibody against gp, the measured serum anti-gp response was comparable to that observed in other CMV vaccine studies. Interestingly, no CMV-seropositive individual developed appreciable anti-gp antibody, and a small fraction of the CMV-seronegative individuals developed an anti-gp antibody response. Antibody levels peaked around weeks 12–16 after vaccination. It will be of interest to determine why CMV-seropositive individuals do not seem to mount a humoral response when reexposed to gp antigen and whether this response can be induced via additional vaccine doses or through a prime-boost strategy with other CMV vaccines.

T cell responses to VCL-CB01 were evaluated by pp65 ex vivo interferon (IFN)- γ enzyme-linked immunospot (ELISPOT) assays. They were considered to be positive if >50 $\text{sfu}/1 \times 10^6$ peripheral blood mononuclear cells were present or there was a >2-fold increase in spot-forming units relative to that seen in controls. T

cell responses were measured at several time points up to 16 weeks after vaccination. In CMV-seropositive individuals, 12.9%–37.9% had a T cell response to pp65, compared with 25.0%–50.0% of CMV-seronegative individuals; responses peaked at weeks 10–12 after vaccination. This response, too, is modest, faring better than the live recombinant CMV Towne/Toledo chimeric vaccines that failed to induce T cell responses [16] but not as well as the Towne CMV vaccine that showed a 45%–69% IFN- γ CD8⁺ T cell response with or without recombinant human interleukin-12 [25].

The highlight of Wloch et al.'s study is the use of the cultured IFN- γ ELISPOT assay to evaluate whether VCL-CB01 primed the T cell memory response at week 32, or 24 weeks after vaccination. The authors found a positive response to pp65 in 63.6% (14/22) and to gp in 59.1% (13/22) of CMV-seronegative participants, with 68.2% subjects (15/22) overall responding to either antigen. This strongly suggests that VCL-CB01 has the ability to prime T cells, such that, on rechallenge with antigen, antigen-specific T cells can proliferate and secrete IFN- γ . Moreover, a persistent response was observed when tested at weeks 16 and 32 in those subjects who received the 5-mg dose.

In all, the VCL-CB01 vaccine at the 5-mg dose with a 3-dose schedule at weeks 0, 2, and 8 holds promise, because it elicits appropriate immunologic responses with typical AEs in CMV-seronegative individuals. Additional studies evaluating its effectiveness in preventing CMV infection and disease and the duration of immunity should be pursued. A limitation of current CMV vaccines being studied is the lack of immune response to vaccine in seropositive individuals. CMV disease in transplant recipients may result from primary infection or reactivation. Moreover, there is an increased risk of developing disease in those who are CMV-seropositive [26]. Seropositivity has been associated with stable levels of CMV-specific CD4⁺ T cells, suggesting an appropriate humoral and cellular response to CMV infection in long-term renal transplant recipients [27]. Interestingly, the

CMV vaccines studied to date, including VCL-CB01, have shown no to minimal immunologic responses in CMV-seropositive individuals. Further studies attempting to increase immunogenicity or identify other CMV antigens associated with disease in seropositive individuals would be beneficial.

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A Cytomegalovirus Vaccine for Transplantation: Are We Closer?

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(See the article by Wloch et al. on pages 1634–1642.)

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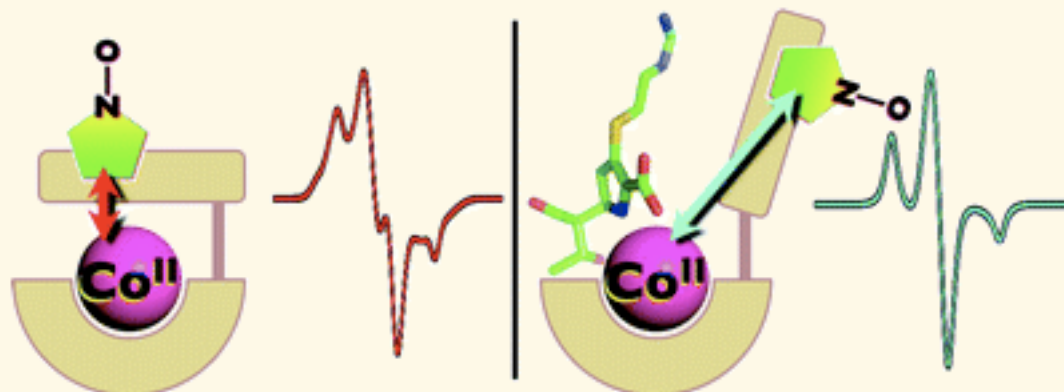
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87 lines (7,839 characters) of back matter

Conformational Changes in the Metallo- β -lactamase ImiS During the Catalytic Reaction: An EPR Spectrokinetic Study of Co(II)-Spin Label Interactions

Narayan Sharma, Zhenxin Hu, Michael W. Crowder, and Brian Bennett

Web Release Date: 04-Jun-2008; (Article) DOI: [10.1021/ja0774562](https://doi.org/10.1021/ja0774562)



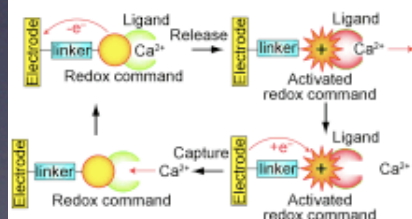
[Abstract](#) Full: [HTML](#) / [PDF](#) (675K)

Electrochemically Driven Release of Picomole Amounts of Calcium Ions with Temporal and Spatial Resolution (p NA)

Christian Amatore, Damiano Genovese, Emmanuel Maisonhaute, Nouredine Raouafi, Bernd Schöllhorn

Published Online: Jun 2 2008 9:03AM

DOI: [10.1002/anie.200705274](https://doi.org/10.1002/anie.200705274)



Controlled delivery: Redox commutation of a paraphenylenediamine and aza-crown ether assembly anchored as a self-assembled monolayer to an electrode surface allows the time and spatially controlled release of picomole amounts of calcium ions. The release occurs on a sub-millisecond time scale, and is irreversible provided that the two-electron-oxidized redox center is not returned electrochemically to its neutral initial state (see scheme).



Database CSA Illustrata: Natural Sciences

Title **The Antarctic-Magellan connection: *Macrobenthos* ecology on the shelf and upper slope, a progress report**

Author [Arntz, WE](#); [Thalje, S](#); [Gerdes, D](#); [Gill, J-M](#); [Gutt, J](#); [Jacob, U](#); [Montiel, A](#); [Orejas, C](#); [Teixido, N](#)

Source The Magellan-Antarctic Connection: Links and Frontiers at Southern High Latitudes. suppl 2, pp. 237-269. Scientia Marina (Barcelona) [Sci. Mar. (Barc.)]. Vol. 69, suppl 2.

Objects



Figure 1.



Figure 2.



Figure 3.

“Figures and tables represent the distilled essence of research communicated in academic articles. Although the analysis contained in the surrounding text is important, it is clear that researchers are eager to view the actual data collected, observed, or modeled to determine the article’s relevance to their own work.”

Problems emerge

- What do we mean by “metadata?”
 - Anything and everything that describes content—including the content itself
- How do we control all of these formats?
 - We haven’t even started to look at output formats (consumers)

Consumers

- Much more varied than the providers, but by and large have the same basic needs
- Many legacy applications/workflows rely on aging formats and protocols
- Some are not sophisticated enough to handle rich metadata
- Title-level metadata only in some cases (not getting down to the item level)

Consumers

- A&Is (various)
- Aggregators (various, but chiefly NLM)
- Archivers (various, but chiefly NLM)
- Booksellers (ONIX)
- CrossRef (CrossRef XML)
- End-users (various)
- Google (NLM)
- Libraries (MARC, Dublin Core via OAI-PMH, OpenURL)
- Subscription agents (ONIX SRN)

- And many more...

End-users as consumers

- End-users consume metadata in more ways than you may think
 - RSS
 - Citation export
 - Social bookmarking
 - Federated search

Ref. mgmt. software

- BibTeX
- EndNote
- ProCite
- Reference Manager

BibTeX

```
@article{  
author = {Go,Vera and Pollard,Richard B.},  
title = {A Cytomegalovirus Vaccine for Transplantation:Are We Closer?},  
journal = {The Journal of Infectious Diseases},  
volume = {197},  
number = {12},  
pages = {1631-1633},  
year = {2008},  
doi = {10.1086/588386},  
URL = {http://dx.doi.org/10.1086/588386},  
eprint = {http://dx.doi.org/10.1086/588386}  
}
```

EndNote

%0 Journal Article
%A Go,Vera
%A Pollard,Richard B.
%T A Cytomegalovirus Vaccine for Transplantation:Are We Closer?
%D 2008
%J The Journal of Infectious Diseases
%P 1631-1633
%V 197
%N 12
%R doi:10.1086/588386
%U <http://dx.doi.org/10.1086/588386>

ProCite

PT - JOUR

AI - Go,Vera

AI - Pollard,Richard B.

TI - A Cytomegalovirus Vaccine for Transplantation:Are We Closer?

YI - 2008

JF - The Journal of Infectious Diseases

JO - The Journal of Infectious Diseases

SP - 1631

EP - 1633

VL - 197

IS - 12

M3 - doi:10.1086/588386

UR - <http://dx.doi.org/10.1086/588386>

Reference Manager

TY - JOUR

AI - Go,Vera

AI - Pollard,Richard B.

TI - A Cytomegalovirus Vaccine for Transplantation:Are We Closer?

YI - 2008/06/167

JF - The Journal of Infectious Diseases

JO - The Journal of Infectious Diseases

SP - 1631

EP - 1633

VL - 197

IS - 12

NI - doi: 10.1086/588386

UR - <http://dx.doi.org/10.1086/588386>

| Software | BibTeX | Endnote/Refer/BibIX | Medline | MODS XML | RIS | Other |
|-------------------|--------|---------------------|---------|----------|-----|--|
| 2collab | Yes | No | No | No | Yes | CSV [6] |
| Aigaion | Yes | No | No | No | Yes | none |
| BibDesk | Yes | No | Yes | Yes | Yes | Endnote XML |
| Biblioscape | Yes | Yes | Yes | No | Yes | none |
| BibSonomy | Yes | Yes | No | No | Yes | various [7] |
| Bibus | Yes | Yes | Yes | No | Yes | SQLite |
| CiteULike | Yes | No | No | No | Yes | COinS |
| Connotea | Yes | Yes | No | Yes | Yes | RDF |
| EndNote | Yes | Yes | Yes | No | Yes | various [8] |
| JabRef | Yes | Yes | No | Yes | No | BibTeXML, DocBook, OpenDocument for OO.o |
| Papers | Yes | Yes | No | No | Yes | Bookends, CSV, Endnote XML |
| ProCite | No | No | No | No | Yes | none |
| Pybliographer | Yes | Yes | Yes | No | No | Ovid |
| refbase | Yes | Yes | No | Yes | Yes | COinS, OpenDocument for OO.o, SRW XML via SRU, unAPI, Word XML |
| RefDB | Yes | Yes | No | Yes | Yes | SRW XML via SRU web service, DocBook, TEI |
| Reference Manager | Yes | No | No | No | Yes | MEDLARS, TSV, CSV, Reference Manager XML, user-customizable |
| RefWorks | Yes | No | No | No | Yes | various [9] |
| Scholar's Aid | No | ? | No | No | No | user-customizable |
| Sente | Yes | Yes | No | No | Yes | user-customizable |
| Zotero | Yes | Yes | No | Yes | Yes | RDF, Wikipedia citation templates |
| Software | BibTeX | Endnote/Refer/BibIX | Medline | MODS XML | RIS | Other |

http://en.wikipedia.org/wiki/Comparison_of_reference_management_software

Problems

- Too many formats
- Too many exchange protocols
- Too much metadata being lost

- Reference management software is an exception

Path dependence

- “A social process grounded in a dynamic of ‘increasing returns’” *Am. Pol. Sci. Rev.* 2000, 94(2): 251-267
 - QWERTY
 - VHS
 - MARC
 - More than 10 variations
 - NLM

A CrossRef solution?

- CrossRef already holds authoritative metadata for the majority of journals
 - In a single, unified XML schema for maximum interoperability
- Could easily expose this metadata to the various consumers in the formats required
- Publishers would eliminate a lot of complexity if they agreed to this

What must vendors do?

- Leverage standards (XML and XSL) to ease ingestion, transformation, and syndication
- Encourage interoperability by using the NLM DTD whenever possible
- Support a multitude of exchange protocols (consolidation is not happening soon)
- Participate in industry forums like this one to understand the needs

How can NISO help?

- Standards are critical in the provision and consumption of metadata
 - Formats, e.g., NLM DTD
 - Exchange mechanisms
 - Unique identifiers (DOI)
- Continuing to bring providers and consumers together to communicate

If you are a consumer of our clients' metadata, and you don't think they're doing a good enough job of getting it to you in the way you need it (or if you have a request for enhancing the flow of information), let us know.



Thank you

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