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*MDL<sup>®</sup> Assay Explorer<sup>®</sup> at Stanford*

Integrated MDL technology plays key  
role in new academic HTS Center

*Discovery Insights*

Managing data warehousing with MDL<sup>®</sup> Isentris<sup>®</sup>

*MDL<sup>®</sup> Patent Chemistry Database*

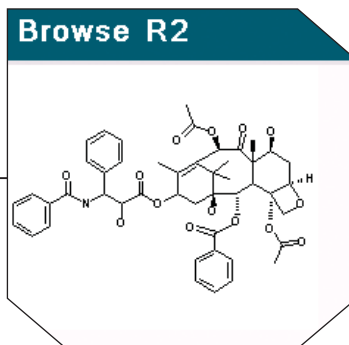
Better bioactivity profiling

*MDL<sup>®</sup> Notebook*

New-generation  
ELN on fast track



Bioactivity Data	
Class of Effect	Pharmacology
Effect	antiviral
Type	IC50
Value of Type (mole conc-unit)	1.2 μmol
Species (Scientific Name)	HCMV polymerase
Method Details	polymerase inhibition; DMSO; dilution
Results	inhibition of virus polymerase, IC50%
Location in Patent	Page column 7-9
Ref 1 Frontpage/Claim: 253; Fulltext: <a href="#">Link</a>	
B1 (2002/01022); Appt: US2000-872	
Application Data	
Area of Use	Pharmaceuticals
Use	Antiviral drug
Indicated Route of Application	herpesviral infection, and cytomegalovirus
Usual Dosage	1-30 mg/kg
Patent	Page column 2-6



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Making data warehousing easy and manageable on the MDL® Isentris® platform

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# MDL<sup>®</sup> Assay Explorer<sup>®</sup> goes to school

## Stanford's High-Throughput Bioscience Center swings into high gear

**MDL** software solutions are playing a vital role at the Stanford School of Medicine, where researchers are developing a world-class center for high-throughput screening and the advancement of chemical biology research.

The School's High-Throughput Bioscience Center (HTBC), established in September 2003 by Professor James Chen, is enabling researchers at Stanford and other institutions to systematically and comprehensively study large numbers of genes and compounds by exploiting the latest high-throughput liquid handling and data acquisition techniques.

Researchers have recently used an MDL<sup>®</sup> Select suite of informatics and experiment management tools to screen Renal Cell Carcinoma (RCC) cell lines for sensitivity to a series of compounds.

Dr. David E. Solow-Cordero, who came to Stanford 18 months ago after working for eight years in the biotech industry, is associate director of the HTBC. He's responsible for managing the facility's day-to-day operations and assisting researchers with assay development and data management. "While pharmaceutical firms have been using high-throughput labs for about 10 years, the first academic involvement with HTS began at Harvard University about seven years ago," said Solow-Cordero. "In the past two to three years its use has accelerated in academia, and many major educational institutions now run HTS centers."

Though assay development in academia is now more common, its scope differs somewhat from that in industry, according to Solow-Cordero. "Most pharmas will only go after a target if there's a \$300 million/year drug at the end of the



*Researchers have recently used an MDL<sup>®</sup> Select suite of informatics and experiment management tools to screen Renal Cell Carcinoma (RCC) cell lines for sensitivity to a series of compounds.*

### The MDL<sup>®</sup> Select advantage

MDL Select workflow tools can be tailored to meet the specific needs of researchers in small to mid-sized biopharmas and academia, enabling them to take advantage of the same scalable discovery informatics solutions employed by global R&D organizations.

pipeline, which invariably involves extremely high throughputs. Where research companies might have 10 to 20 scientists working on a project, an academic lab is more likely to have just a couple of people."

Academic labs are less intent on screening a million compounds a week, he says. "If an academic lab does a couple dozen screens a year, and 10 years later one of them leads to treatment of a rare disease or parasite that the pharmaceutical industry has not invested in, then the lab has done its job."

On the other hand, academic researchers need to follow the same stringent protocols as their colleagues in industry. This means validating results with statistical analysis and running good secondary assays to show specificity, according to Solow-Cordero. "I work hard to inject these kind of positive workflow practices from my industry experience into the assay development process at Stanford."

### Up and running

Thanks to Solow-Cordero's efforts, the Stanford HTBC is now fully functional with all instrumentation purchased and installed. The compound libraries are in and formatted and the HTS databases are complete.

The Center's databases are built in the MDL<sup>®</sup> ISIS environment—augmented by MDL<sup>®</sup> Direct (data cartridges), MDL<sup>®</sup> Draw chemical drawing and rendering software and the MDL<sup>®</sup> Cheshire suite of chemical structure manipulation and analysis tools.

MDL<sup>®</sup> ChemBio AE provides chemical registration services and an integrated

*(continued on page 4)*

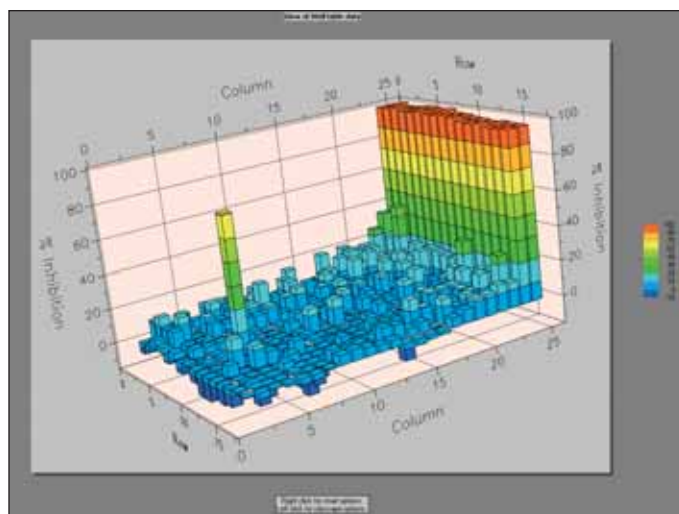
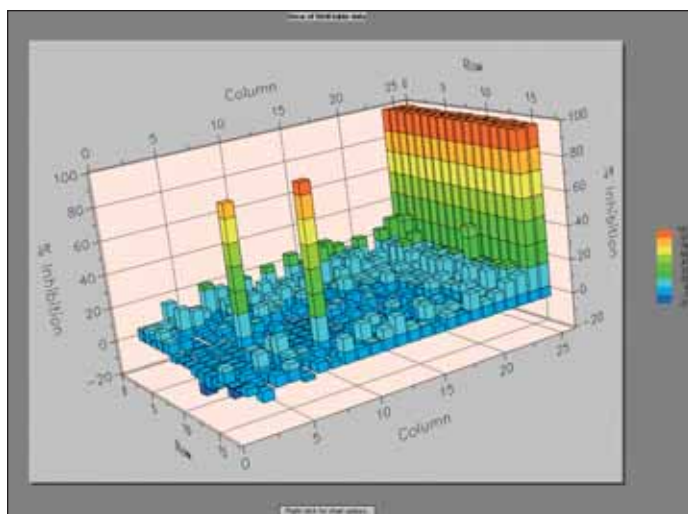


Figure 1: Cityscape views in MDL Assay Explorer showing two positive compounds in the minus cell line (RCC/VHL-) and one positive compound in the plus cell line (RCC/VHL+)

*“What’s great about the current MDL system at the HTBC is that it’s fully integrated, so I can go from compound to compound plate to assay plate results to reporting, all using essentially an out-of-the-box solution.”*

*Dr. David Solow-Cordero  
Associate Director  
Stanford HTBC*

retrieval and viewing solution for chemical and biological data. The MDL® Plate Manager system provides a fully integrated central repository for plate and sample information. Finally, the MDL® Report Manager tool lets researchers extract and organize complex HTS information into a broad range of reports for information sharing and collaboration.

The primary workhorse for managing the biological aspects of HTS is the MDL® Assay Explorer® biological data management system. Assay Explorer captures, analyzes and stores experimental results in an Oracle® environment.

“MDL Assay Explorer, the core component of our MDL database system, is currently storing all our HTS data, retest data and IC50/EC50 results,” said Solow-Cordero. “We’re looking forward to adding ADME/Tox and *in vivo* data

in the future, and I’m also looking for ways to integrate high-content image analyses.”

“When I was working in industry, I used MDL ISIS/Base and ISIS/Host, creating my own Oracle tables for HTS data analysis. What’s great about the current MDL system at the HTBC is that it’s fully integrated, so I can go from compound to compound plate to assay plate results to reporting, all using essentially an out-of-the-box solution.”

#### The inaugural project

The Center’s first HTS project targeted Renal Cell Carcinoma (RCC), which is fatal in 40% of the 31,000 new cases diagnosed in the U.S. every year.

The project involved the parallel screening of RCC cell lines (matched for VHL expression)

## Stanford’s High-Throughput Bioscience Center

### Comprehensive screening of biological systems

#### Instrumentation available at the HTBC

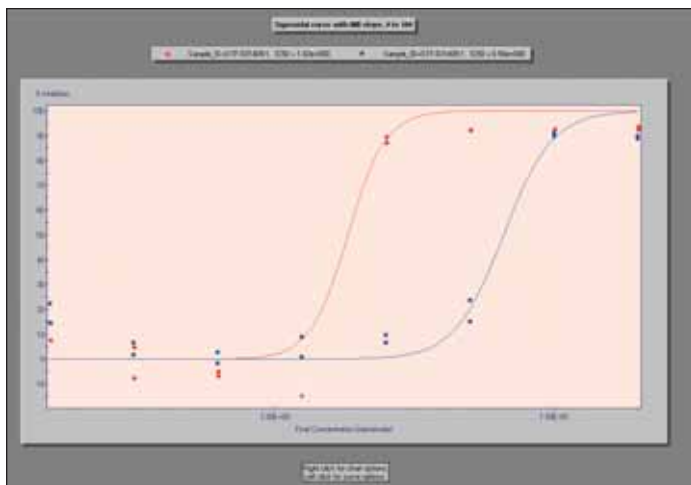
The Center houses a fully automated, integrated instrumentation system for high-throughput liquid handling, high-throughput detection and high-content enzyme-/protein- and cell-based screening. The liquid-handling robot can manipulate and pipet volumes to up to 200 384-well plates, which can be stocked with various ingredients, including living cells. Researchers can then add a different gene or chemical compound to each well, simultaneously testing thousands of conditions. The

integrated, multi-mode plate reader measures the wells’ absorbance, fluorescence, chemiluminescence or other desired characteristics. In addition, a high-content cellular imaging and analysis system enables researchers to take digital pictures of each well using a fully automated inverted epifluorescence microscope that is capable of recording multiple fluorescent images of fixed and live cells in a few minutes.

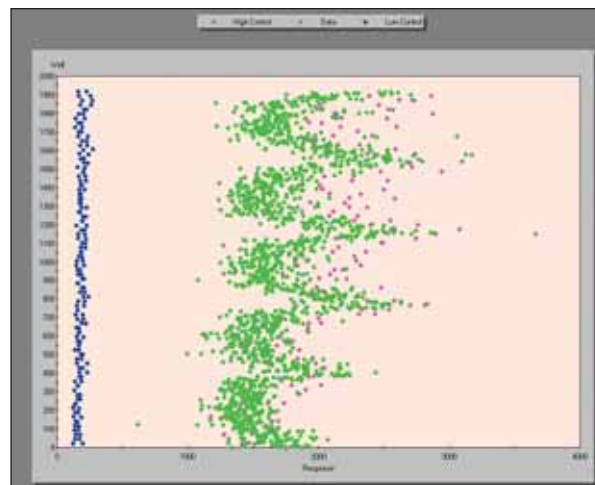
#### Services at the HTBC

Utilizing the HTBC, researchers can perform systematic screens of biological systems using

cDNA libraries for *in vivo* or *in vitro* protein expression, siRNA libraries for targeted gene silencing and chemical libraries for the identification of small molecule modulators of specific biological processes. The Center’s compound library currently contains 64,000 compounds, but this number is expected to double in a short time. The library focuses on diversity with the expectation that researchers should be able to run any sort of assay possible, with a reasonable expectation of finding an agonist and antagonist for any



*Figure 2: Dose response curves in MDL Assay Explorer showing differential in cell activity between minus and plus cell lines for a screen*



*Figure 3: Scattergram in MDL Assay Explorer showing pronounced edge effects in luminescence cell-based screen (Plates 1-5, 1 on bottom)*

for sensitivity to a series of compounds. Hypothesizing that the difference in transcriptional states between VHL-deficient and VHL-positive cells could be exploited for a positive therapeutic response, researchers developed a robust cellular assay and screened 64,000 compounds in 384-well plates.

MDL Assay Explorer tools enabled researchers to select actives, remove outliers, validate the data and identify trends. For example, Assay Explorer's cityscape visualization quickly revealed compounds that were specific for a cell line (refer to Figure 1), ultimately identifying 400 hits, 150 of which retested positive. Dose response curves clearly displayed the differentials in cell activity between minus and plus cell lines (refer to Figure 2). In the end, researchers found 80

compounds selective for RCC/VHL- and 17 selective for RCC/VHL+.

Assay Explorer tools were also useful in displaying trends in the data. Figure 3 is a scattergram of a luminescence cell-based screen that shows significant edge effects moving from Plate 1 on the bottom to Plate 5 at the top. This additional view of all the experimental data highlighted a potentially problematic edge-effect trend, enabling the researchers to stop the experiment, thereby saving both time and precious reagents.

"The MDL Select software suite, anchored by MDL Assay Explorer, is central to the success of the HTBC, because its components integrate so well out-of-the-box" said Solow-Cordero. "HTBC staff will continue to work closely with Elsevier MDL, as we build a

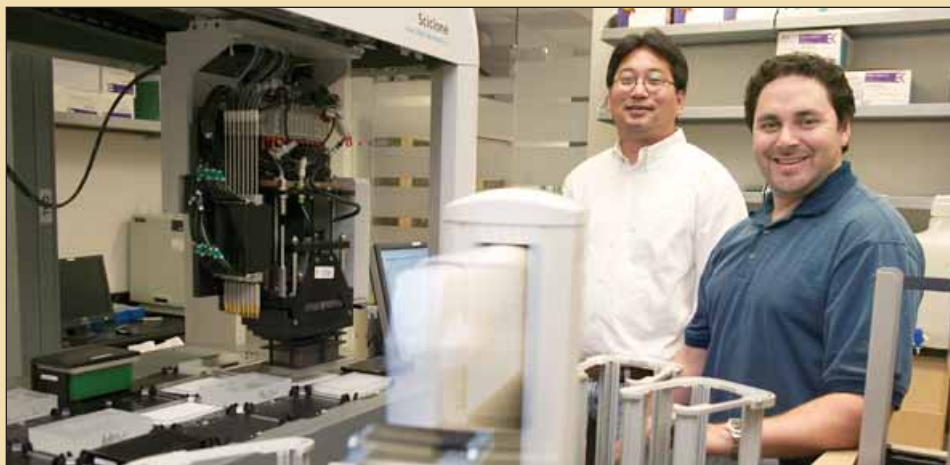
Lab practices evolve quickly. So does MDL Assay Explorer. The 3.0 version, released in July 2005, provides increased flexibility for the scientist and contains impressive performance and integration enhancements. Tailored to biology workflows, this latest release gives biologists the freedom to add conditions and results to data analysis without having to modify templates or request administrator help.

world-class center for advancing the molecular and cellular understanding of human health and disease." ■

assay. Assuming the use of 384-well micro-plates, estimated throughput performance is 100,000 enzyme assays and 50,000 cell-based assays per week. The emphasis is less on throughput than on flexibility—the ability to run many different types of enzyme- and cell-based assays in a single integrated system.

#### Funding of the Center

Originally funded by the Department of Molecular Pharmacology at Stanford and the National Institutes of Health, the HTBC is housed in space provided by the Stanford School of Medicine. It is expected that the Center will be self-supporting with the help of user fees, grants and donations. For more information, visit <http://htbc.stanford.edu/>. ■



*James Chen, Ph.D., assistant professor of molecular pharmacology, and David Solow-Cordero, Ph.D., associate director of the High-Throughput Bioscience Center, Stanford University School of Medicine, Department of Molecular Pharmacology (photo courtesy of Stanford Office of Communication & Public Affairs)*

# Beyond Data Warehousing

## Improving information access with MDL® ISENTRIS® technology

```
a_acc
a_aro
a_don
a_heavy
a_nBr
a_nC
Apol
b_1rotN
b_triple
balabanJ
Bpol
chi0
Density
Fcharge
Kier1
KierA3
KierFlex
Mr
PC-
PC+
PEOE_PC-
PEOE_PC+
PEOE_RPC-
PEOE_RPC+
PEOE_VSA+
PEOE_VSA_HYD
etc
```

Figure 1: A typical display from a data warehouse includes a long list of fields that can be difficult for researchers to query and browse.

```
+ Atom Counts
+ Bond Counts
- Charge Descriptors
  PC+
  PC-
  PEOE_PC+
  PEOE_PC-
  PEOE_RPC+
  PEOE_RPC-
  PEOE_VSA+0
  PEOE_VSA+1
  PEOE_VSA+2
  PEOE_VSA+3
  etc
+ Connectivity Indices.
+ Graph distance matrix
+ Kier Kappa Shape Indices
+ Pharmacophore Atom Types
- Physical Property
  Mr
  Apol
  Bpol
  Density
  Vdw_area
  Vdw_vol
```

Figure 2: ISENTRIS presents data for querying and browsing in defined groups (tables), enabling easy navigation, query building and browsing.

Data warehouses consolidate information, enabling researchers to access disparate data rapidly with simple queries. However, while warehouses may solve certain data access problems, they also create formidable challenges.

For instance, warehouses often flatten the data into simplified views and require researchers to navigate through many data fields, which can be difficult to browse and often contain redundant data. Furthermore, researchers cannot be certain that a warehouse is up to date as the addition of new data frequently requires time-consuming administrative support and overnight processing.

These same challenges also make it difficult for developers and administrators to manage data warehouses. Adding individual variables to a database typically requires updating the views and forms associated with the warehouse. Frequent requests for new data and calculations tie up resources. Lengthy

processing times leave large warehouses offline when researchers need them the most.

MDL® ISENTRIS® technology addresses these challenges, making data warehousing more responsive to researchers' needs and easier for developers and administrators to manage.

### Simplified data navigation

As shown in Figure 1, data warehouses handle the problem of multiple data silos by flattening query data into long lists of fields. Warehouse browse forms typically present results in large tables. Techniques like this inhibit an efficient workflow.

ISENTRIS makes navigation and query building simple, fast and intuitive for researchers by automatically pre-filtering and grouping lists of fields into domains (refer to Figure 2). ISENTRIS browse forms also automatically group data into tables, removing redundancies and presenting results in the correct context.

The screenshot shows the 'Browse R1' interface for the sample 'CBAE-006792'. On the left, a 'Field Selector' lists various fields categorized by groups like 'Atom Counts', 'Bond Counts', 'Charge Descriptors', 'Connectivity Indices', 'Graph distance matrix', 'Kier Kappa Shape Indices', 'Pharmacophore Atom Types', and 'Physical Property'. The main area displays a table of properties for the selected sample:

Corporate Number	CBAE-006792	Molecular Weight	183.21
HAcceptorCount	2.00		
HeteroAtomCount	4.00		
LargestRClusterSize	6.00		
ChargedFragmentSize	0.00		
LargestFragmentSize	14.00		
StereoCenterCount	2.00		

Below the table, there are three molecular structure visualizations: 'HAcceptorHMol', 'LargestRClusterHMol', and 'StereoCenterHMol'. At the bottom, a 'PivotedResults' table shows data for the sample:

Sample_ID	CDK2 IC50	Caco-2 IC50	EGFR IC50	HIV-1 Nef/Hck IC50	PKCa IC50
1	0.726				19.3

Figure 3: With MDL Cheshire, researchers can create additional chemical information on-the-fly in support of data analysis.

*Isestris makes data warehousing more responsive to researchers' needs and easier for developers and administrators to manage.*

### Self service data access

Researchers accessing a data warehouse can select from a large, complex array of data. However, the static query and browse forms often encountered in the warehouse environment impose significant limitations. The query interface may show too much data, complicating searches. There may be redundancies or unwanted data in the returned results.

Self-service data access in Isestris lets researchers build and save their own query forms—optimized for particular types of searches. Isestris even returns data in the context of a query using an automatically generated browse form. If researchers are missing information from a warehouse, they can drag and drop the data onto the form for self-service browsing or generate additional data with third party or custom calculators.

Isestris also supports list logic, cherry-picking, table forms and sorting, enabling researchers to further explore the diversity of data within a warehouse using a single application.

### Real-time data access

Researchers are often interested in investigating the relationships between different data points in a vast warehouse collection. These analyses can require computations between two or more fields. If researchers want to calculate additional data, they have two options: request that administrators update the warehouse with the information, or export the data from the warehouse and use other tools to process the data. Both options interrupt the workflow.

Isestris offers a powerful interface for accessing data and the ability to integrate with other analysis tools. Integrating custom or vendor calculators such as MDL<sup>®</sup> Cheshire, as shown in Figure 3, can reduce the need to

push data to other applications and eliminate the wait for administrators to update the warehouse with new data. Researchers simply define the calculations they want between the appropriate data fields, and these become accessible without administrative support. Researchers can access the data they want when they want it—and create useful data on-the-fly to support decision making (refer to Figure 4).

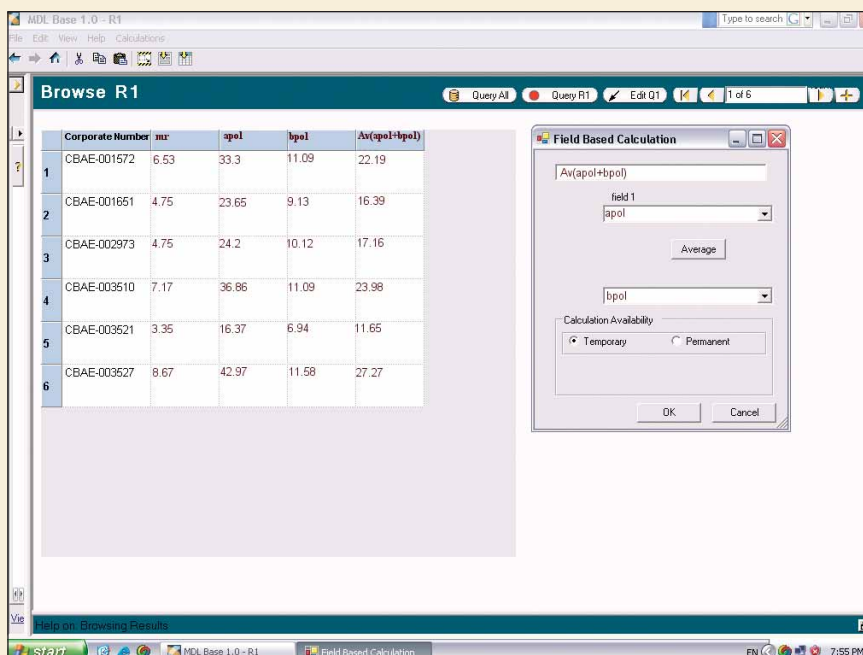
### Instant updates, minimal support

To handle regular additions of data, warehouses require continual indexing, processing and management. This maintenance is usually performed offline at times when researchers don't require data access. It may take up to a day for researchers to be able to query experimental data in the context of warehouse data. Certainly, as databases get larger, the window of opportunity to complete these updates gets smaller, and in severe cases warehouse data may not be available at all for extended periods. Further issues arise when adding data (such as assays, projects and variables) requires warehouse structure, view and application changes. Administrative delays like these translate directly into research delays.

Isestris greatly streamlines database maintenance and updates. Isestris tools enable warehouse administrators to update data views automatically and create views that reduce the need for pivoting data. With Isestris, when new data fields are added to the warehouse, they are instantly available to researchers. Isestris also enables researchers to access “virtual data,” further reducing the amount of data that administrators need to process.

### Build a better warehouse

By introducing self-service, customization and flexibility to the practice of data warehousing, MDL Isestris technology improves the effectiveness of discovery warehouses. MDL Isestris can make it easier than ever for researchers to access the large stores of data generated in discovery R&D. At the same time Isestris overcomes the traditional maintenance and upkeep challenges associated with warehouses, allowing IT specialists to deliver researchers the information systems they need in a timely manner. ■



*Figure 4: A custom dialogue in an MDL Base browse form enables researchers to select the fields and calculations they wish to run. The browse form in the background shows the new computed field with the warehouse data.*

# Better bioactivity profiling

## Export bioactivity data from MDL<sup>®</sup> Patent Chemistry Database

The ability to quickly find property data for substances of interest and create structure-activity relationship (SAR) tables is important to researchers in the lead discovery process.

This At the Bench demonstrates this type of bioactivity profiling with MDL Patent Chemistry Database, using the MDL<sup>®</sup> CrossFire<sup>®</sup> Commander browser.

### How to search substances and their data

Figure 1 illustrates how to find substance data in the Patent Chemistry Database.

- 1 Click **Select Database** and choose **Patent Chemistry Database** from the menu.
- 2 Click **Draw Structure** and then enter the substance query.
- 3 For a substructure search, select **all atoms** under **Free Sites**.
- 4 Check **Allow related Markush** to get Markush structures that are related to your specific hit structures included in the hit set (this is not a Markush structure search).
- 5 **Data Search:** See the fields in the hierarchy tree, which are indexed in the area of bioactivity/application data.
- 6 Next to **Search Context**, select **Substances**.
- 7 Click **Start Search**.

### Viewing the bioactivity and application data of a specific hit substance

Bioactivity Data	
Class of Effect	Pharmacology
Effect	antiviral
Type	IC50 <b>1</b>
Value of Type (mole conc.-unit)	1.2 µmol/l
Species (Scientific Name)	HCMV polymerase
Method Details	polymerase inhibition; DMSO; dithioth
Results	inhibition of virus polymerase, IC50&sub
Location in Patent	Page column 7-8 <b>2</b>
Ref. 1	Frontpage/Claim: <b>253</b> , Fulltext: <b>Hit link</b> ; Patent: Pharmacia and Upjohn Company, Publ.: US6340680 B1 (2002/01/22), Appl.: US2000-672472 (2000/09/28)
Application Data	
Area of Use	Pharmaceuticals
Use	Antiviral drug
	compound of a pharmaceutically acceptable salt thereof is useful for treating or preventing a herpesviral infection and cytomegalovirus (CMV) in a mammal
Preferred Route of Application	parenteral, topical, oral, rectal
Preferred Dosage	1 - 30 mg/kg
Location in Patent	Page column 2.8 <b>3</b> <b>4</b>
Ref. 1	Frontpage/Claim: <b>253</b> , Fulltext: <b>Hit link</b> ; Patent: Pharmacia and Upjohn Company, Publ.: US6340680 B1 (2002/01/22), Appl.: US2000-672472 (2000/09/28)

Figure 2 shows a substance hit record from the search in Figure 1, including measured bioactivity and application data described in patents published since December 2003.

Besides the inhibition concentration shown here [**1**: Type=IC50], the bioactivity data field also may include effective concentrations (EC50), binding constants for protein-ligand-interactions ( $K_i$ ), lethal doses (e.g. LD50) and other parameters.

The record shown includes the **Location in Patent** **2**, which is the page of the bioassay in the original publication, a **frontpage/claim link** **3** to the database citation record and a link **4** to the original document at a patent provider (e.g. EspaceNet, US Patent Server, MicroPatent, Delphion).

# Chemistry Database to SAR tables

## Including the related Markush structures in a hit set

From December 2003 onwards specific substances—real or “prophetic” compounds—are linked to the corresponding “Related Markush Structure” in a given patent publication during the indexing process. Selecting the query option **Allow related Markush** includes these related Markush structures in the hit set. *Note: This is not a Markush structure search.*

**Patent-Specific Data**

Compound Identifier in Patent B-7  
Related Markush Structure (PRN) 179350

Ref. 1 Frontpage/Claim: 253, Fulltext: [Link](#); Patent Pharm B1 (2002/01/22), Appl.: US2000-672472 (2000/09/28)

PRN=179350

Compressed MARKUSH: Right-click to expand details

Copy to Report Print

Label	Value	Size	Attributes	Substituted by	Frequency
R1	alkyl	1-6C	optionally substituted, top		
R2	OH				
alkoxy	1-4C				
heterocycl	3-6		4,2 S, N, O		

Figure 3

In addition to the bioactivity data, the hit substance of Figure 2 shows **Patent-Specific Data** illustrating the **Compound Identifier in Patent** (2) label. In this case it is B-7, which the inventor used in the document to describe the specific compound (1).

Also shown is the **Related Markush Structure** (3), of which the hit substance is a representative. The corresponding Markush structure image appears in compressed form (4). Right clicking on the compressed form opens an expanded form (5).

## Viewing the Markush Family

**Substance Characterization**

Patent Compound Registry Number 179350  
Substance Type **Markush**  
organic compound

Referencing Compounds [click here](#)  
Compound as Reagent [show reactions](#)

PRN=179350

Compressed MARKUSH: Right-click to expand details

Figure 4

To view other specific examples (real or prophetic) that are representative of the Markush structure (1), click on the Markush link (2) to view the Markush Family (3).

## Exporting bioactivity data to a SAR table

All four compounds shown in Figure 4 have bioactivity data (indicated by the red text “Bio” on top of the structure window) that can be easily exported to a structure-activity-relationship table.

MDL CrossFire Commander - [Patent\_Chemistry(2005/04/Upd.04)001 Sub] 3 of 5

Query Results Alerts Automaton

Substance Characterization

Patent Compound Registry Number 179350  
Chemical Name N-(4-chlorobenzyl)-8-(3-hydroxypropyl)-2,3,4,5-tetrahydro-1H-benzodiazepine  
Molecular Formula C<sub>22</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>4</sub>

Settings...  
Substances (Identification, Bioactivity) to Excel as Table  
Substances (Identification, Bioactivity) to SDfile  
Substances (all Data) to HTML as Table  
Substances (Identification, Bioactivity, Application) to HTML as Report  
Substances (Identification, Phys. Data) to HTML as Report  
Substances (Identification, Application) to HTML as Table

Figure 5 shows how bioactivity data can be exported to a SAR table from the **Results** menu (1) using **Export Hits** (2). You can create your own export formats by clicking on **Settings** (3), or use the predefined export formats (4) delivered with CrossFire Commander 7.0 SP1 covering export to structure-data files (SDfiles), Microsoft Word, Microsoft Excel and HTML. To create a SAR table, use the export format “**Substance (Identification, Bioactivity) to SDfile**” (4) and import the SDfile into MDL® ISIS for EXCEL using the menu options **ISIS** ⇒ **Import** ⇒ **SDfile to worksheet**.

Structure	Compound RegNo	Molecular Formula	Class of Effect	Effect	Type	Value (μMol/l)	Species (Scientific Name)	Location in Patent	Citation
	179350	C <sub>22</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>4</sub>	Pharmacology	antiviral	IC50	1.2	+CMV polymerase	Page column 7-9	US Patent, Pharmacia and Upjohn, <i>Chemistry, 2001</i> , US6340620, B1, (2000/01/22), Appl. US2000-672472 (2000/09/28)

Figure 6 shows one line of the SAR table created for the four Markush Family structures in Figure 4.

Structure	Compound RegNo	Effect	Type	Value (μMol/l)	Species	Test System	Method Name	Location in Patent	Citation
	438188	β-galactosidase inhibition	Ki	330	Saccharomyces sp.	β-galactosidase (EC 3.2.1.23)	Kinetic analysis of β-galactosidase Inhibition Analysis of Glycosidase Inhibition Activity With CZE	Page/Page column sheet 1, 10, 22	248135 Patent, 2005/05/19, 2005/05/20, The Scripps Research Institute, US677440, US, EB, (2004/08/19), 2004, US2002-800863, 2002/02/12, 2002.
	438189	β-galactosidase inhibition	Ki	53	Saccharomyces sp.	β-galactosidase (EC 3.2.1.23)	Kinetic analysis of β-galactosidase Inhibition Analysis of Glycosidase Inhibition Activity With CZE	Page/Page column sheet 1, 10, 22	248135 Patent, 2005/05/19, 2005/05/20, The Scripps Research Institute, US677440, US, EB, (2004/08/19), 2004, US2002-800863, 2002/02/12, 2002.
	438192	β-galactosidase inhibition	Ki	28	Saccharomyces sp.	β-galactosidase (EC 3.2.1.23)	Kinetic analysis of β-galactosidase Inhibition Analysis of Glycosidase Inhibition Activity With CZE	Page/Page column sheet 1, 10, 22	248135 Patent, 2005/05/19, 2005/05/20, The Scripps Research Institute, US677440, US, EB, (2004/08/19), 2004, US2002-800863, 2002/02/12, 2002.

Figure 7 shows another SAR table with protein-ligand-interactions showing the structure (1), the test system (5) (here proteins) and the species (4) together with the effect (2) and the corresponding protein-ligand binding constants  $K_i$  (3). The table also includes the **Location in Patent** (6) where this bioassay appears and the citation (7), including patent assignee and publication/application number and date. ■

# Send your structures to DiscoveryGate®

## See where they take you

Thanks to an innovative new linking capability from Elsevier MDL, there's even more reason for life sciences companies to make the online DiscoveryGate® content service ([www.discoverygate.com](http://www.discoverygate.com)) their first stop for scientific information and the answers to discovery questions.

Researchers can use the new linking capability to transfer chemical structures from in-house or third party applications (such as an inventory management system or electronic laboratory notebook) directly to DiscoveryGate via a single click in the application. With a DiscoveryGate license in place, researchers can immediately search for transferred compounds on the DiscoveryGate platform, accelerating synthesis planning and decision-making.

### Easy to implement

To implement the linking, Elsevier MDL supplies IT specialists with the software components and documentation to expose a hyperlink in custom applications built on COM, .NET, Java or HTML technology. The molecules are communicated as MDL® Chime Strings with searches conducted over the MDL® Compound Index (which currently indexes 19 diverse databases).

Once the software is installed, scientists can transfer structures of interest as direct queries to DiscoveryGate.

The system runs the following types of structure searches: automatic, exact, substructure search, isomers, tautomers and salts. The automatic search strategy looks for records that match a query using the following combination of search types, moving from a particular to a more general set of search criteria to gradually widen the search until the system finds a hit.

*Transfer chemical structures from in-house or third party applications directly to DiscoveryGate via a single click in the application.*

- 1. Related compounds search:** Searches for related compounds with no additional substitution.
- 2. Exact match search:** Searches for substances that match the structural query exactly.
- 3. Include isomers search:** Searches for all stereoisomers (all *R* and *S* configurations, all *E* and *Z* configurations, and so on).
- 4. Include tautomers search:** Searches for all tautomers, and also for structures with different charges and different isotopes.
- 5. Include salts search:** Searches for substances that include different salts.
- 6. Substructure search:** Searches for substances that contain the query wholly embedded within them.
- 7. Similarity search:** Searches for substances that are structurally similar to the query.

The search workflow also enables researchers to obtain electronic versions of primary literature articles, provided the articles are available in electronic format and the researchers hold the appropriate access rights.

The screenshot shows the MDL Base 1.0 software interface. The main window is titled 'Browse R2' and displays a chemical structure of Taxol. To the right of the structure is a table with the following data:

CDBRegNo	139
Molecule Name	Taxol
Corporate ID	MUSE33300371
Molecular weight	853.93

Below the table, there are navigation tabs: Home, Toxicity Data, NCBI Geo, Assay Data, xPharm, DiscoveryGate, and Scirus. Under the 'DiscoveryGate' tab, there is a section titled 'Find Related Data In DiscoveryGate' which contains a search input field with a dropdown menu set to 'sss' and a 'search in' button, followed by a 'DiscoveryGate' link.

Figure 1: Result screen from search in corporate application in MDL Base environment



# MDL<sup>®</sup> Notebook—

## Turning a new page in collaborative e-R&D

*The new-generation electronic MDL Notebook will help researchers work more efficiently together, save time, reduce costs, focus on science and make better decisions.*

In March 2005 Elsevier MDL announced that it was building a robust, scalable, enterprise-strength electronic laboratory notebook (ELN) for the life sciences with delivery in 2006. Building on a decade-long history of building custom ELNs, the company now plans to deliver the first release of the MDL<sup>®</sup> Notebook application in the fourth quarter of 2005—with a solid demonstration version available in time for the product's official launch at Drug Discovery Technology<sup>®</sup> (Boston) in August.

The electronic MDL Notebook will become the next-generation hub for workflow applications and discovery data on scientists' desktops. Built on MDL<sup>®</sup> Isestris technology, MDL Notebook supports the capture, authentication, integration, reporting and sharing of scientific data and the integration of critical workflow applications. MDL Notebook will help researchers work more efficiently together, save time, reduce costs, focus on science and make better decisions.

The requirements for an effective lab notebook go well beyond capturing the essential what-why-how-when-and-who of discovery research. A desirable system also manages the critical user authentication and audit functions required for due diligence and patent applications. Researchers need the system to generate industry-standard structure and reaction databases and handle transformation searches. They want to query corporate and third party databases as well as their own data. They want an application that interfaces with corporate LIMS, supports multi-site, multi-national operations and is backed by a worldwide customer care organization. On a more mundane level, the system needs to handle a scientist's everyday activities such as cutting and pasting information into Microsoft<sup>®</sup> Word, Excel<sup>®</sup> and PowerPoint<sup>®</sup> documents.

Elsevier MDL has over ten years of experience satisfying these and similar needs, having already built or helped to build more than 15 custom and commercial ELN systems, some of which have been deployed to over 200 researchers. Several thousand scientists around the world are currently using MDL electronic laboratory notebooks.

MDL Notebook will address the needs of discovery scientists, particularly in organic synthetic chemistry, with a scope including authentication, sign/witness, audit, record repository and reporting functions and with support for single-, multi-step and parallel syntheses.

The first release will integrate with MDL structure and reaction registration services, with the MDL<sup>®</sup> Logistics materials management solution, and with both MDL and proprietary customer content. MDL Notebook will also access hosted content via the DiscoveryGate<sup>®</sup> and ScienceDirect<sup>®</sup> platforms.

Subsequent ELN releases in 2006-2007 will provide additional functionality supporting biology and developmental chemistry, in particular analytical chemistry, formulations, pharmacokinetics and ADMET, while also enabling customized laboratory workflows and 21 CFR part 11 compliance.

Elsevier MDL offers extensive experience in developing and delivering ELN consulting applications, deep domain knowledge in chemistry and biology workflows, a large and growing biopharmaceutical customer base, worldwide customer care and a corporate commitment to the pharmaceutical and wider scientific marketplaces. For all of these reasons, Elsevier MDL is well positioned to deliver a next-generation ELN solution that is central to the scientific workflow and energizes discovery R&D. ■

The screenshot shows the MDL Notebook interface with the following components:

- Menu Bar:** File, Edit, View, Tools, Help
- Experiment Details:** Title: First assay of screening; Conclusion: Half finished; Units: mg/ml/nmol; User: GUEST; Chemist: Guest User; Creation Date: 15/05/2005
- Reaction Diagram:** Shows a reaction between an ortho-diaminobenzene derivative (with R1 and R2 substituents) and a glyoxal derivative to form a product.
- Reagent Tables:**
  - ortho-diaminobenzene derivative:**

Name	NB Ref	Quantity	Volume	Mol Wt	Purity %	Ratio	Density
1 ortho-diaminobenzene	216,295	108,143	108,143	1,000	1,000		
2 3,4-diaminophenol	248,284	124,142		1,000			
3 3,4-diaminotoluene	244,340	122,170		1,000			
4 1,2-diamino-4-nitrobenzene	306,290	153,140		1,000			
  - glyoxal derivative:**

Name	NB Ref	Quantity	Volume	Mol Wt	Purity %	Ratio	Density
1 Glyoxal	116,072	58,036	58,036	1,000	1,000		
2 Glyoxylic acid	148,070	74,035		1,000			
3 Glyoxylic peracid	180,068	90,034		1,000			
4 Glyoxylic amide	146,101	73,051		1,000			
- Buttons:** Import..., Clear, Across..., Down..., < Remove, Add, Delete, Experiment Locator, Make Experiment Public, New Experiment, Delete Experiment, Save, Cancel

*Setting up a parallel synthesis experiment. MDL Notebook goes beyond archiving data to actively manage scientific research.*

## Train-the-trainer: Maximizing the benefit of MDL solutions

Elsevier MDL has rolled out a new program that rapidly creates skilled, in-house trainers who can help their colleagues get the most out of MDL tools and applications.

Educational Services unveiled the new model at the US User Conference 2005 in Scottsdale, AZ (see page 14), in a session focusing on searching CrossFire Beilstein. The inaugural class is a template for similar train-the-trainer sessions and can be applied to all end-user courses for other MDL® brand products.

"This program focuses on the needs of in-house trainers," said Peg Renery, Director, Market Development, Educational Services. "As with all of our programs, the course develops new skills through practice and hands-on experience."

The train-the-trainer model allows participants to return to their organizations and teach their colleagues, giving companies the flexibility to

handle further training in-house in a convenient, cost-effective fashion. One participant in the inaugural session in Scottsdale described the experience as "the best money that [my company] ever spent."

Research shows that retention increases seven-fold when people learn by doing. Accordingly, the train-the-trainer program gives students opportunities to coach one another, get hands-on experience with the software and exercise their presentation skills.

Michelle Kuo of Merck clearly saw the value. "I think train-the-trainer will enable me to provide more useful training and problem solving," she said.

Barbara Greenman of the University of Colorado added: "I'm hoping to set up a user session once every semester. I'd like to tailor it for undergraduates since they are using it and

becoming more savvy with the electronic databases."

The train-the-trainer program complements the new Elsevier MDL Learning Center, which provides self-paced tutorials and printable materials that are accessible at any time. In-house instructors can use the Learning Center to support their internal training, and students can augment their classroom experience by returning on their own to the Learning Center for advanced training or self-paced tutorials. (For more information on the Learning Center, see *Molecular Connection*, Vol. 23, No. 1, 2005.)

For more information on train-the-trainer courses or to schedule a course, contact your Elsevier MDL Account Manager or Peg Renery at p.renery@mdl.com or 800-955-0051, ext. 1377. ■

## Online Ordering—Make a Quick Purchase

Elsevier MDL recently launched an online ordering service to make licensing MDL® products easier and quicker for customers. This option is designed for customers who simply wish to license a single copy of selected MDL content for access via DiscoveryGate® or desktop stand-alone software products. It is ideal for employees of life science and chemical companies, as well as academics who want to pay using a credit card.

To access this service, simply go to [http://www.mdl.com/online\\_order/](http://www.mdl.com/online_order/). The Web page lists the available content and framework products from Elsevier MDL, which include: DiscoveryGate®, Integrated Major Reference Works, MDL® Available Chemicals Directory, MDL® Patent Chemistry Database, xPharm®, and MDL ISIS stand-alone software including: MDL® ISIS for Excel, MDL® ISIS/Base, MDL® ISIS/Draw and MDL® Sculpt.

### How do I order?

Ordering is simple. After you have decided what to purchase, simply scroll down to the bottom of the page and click on the link to order products. This will take you to the appropriate online order form where you can make your selections and add them to the cart with a single click. A variety of credit cards are accepted. After filling in the Online Order Shopping Cart fields, submit the form, credit card number and license, and your order, once processed and accepted, will arrive via FedEx for products ordered within the United States or via DHL for international orders.

### How long does it take?

Since the entire transaction including payment verification and licensing is done online, you can expect to receive your processed order in two

business days. This is in contrast to the normal time of five or six business days using a paper-based system.

### Will Elsevier MDL offer more products in the future?

We plan to offer more of our products and databases accessed through DiscoveryGate in the near future, with the ultimate goal of offering as many of our products and services via online ordering as will benefit our customers. For more information, visit [www.mdl.com](http://www.mdl.com). Happy e-shopping! ■

## Road trip!

Members of Elsevier MDL's executive team recently took to the road in the U.S. and Europe to provide focused half-day strategic updates for customers. The U.S. briefings were given in San Francisco, San Diego, Philadelphia and Boston, and the European sessions were in Paris, Frankfurt, Basel and London. The meetings attracted a

wide range of customers from large pharma and small and mid-sized biopharma companies.

Customers heard from CEO Lars Barfod, who described Elsevier MDL's overall vision and strategy, and were given more detailed updates in the company's three main solution areas: framework (Victoria Rehn), workflow (Trevor Heritage) and content (Steve Young). There was

also an update on Elsevier MDL's research program, and Jean Colombel (Life Sciences Sales and Services) rounded out the session by describing customer support, training and consulting services.

The briefings were well received by customers and are likely to become a regular occurrence. ■

*"I really enjoyed the accessibility to Elsevier MDL's real decision makers. It's refreshing to feel that our small company concerns were taken seriously and addressed."*

Margot Goodwin, Emisphere Technologies (US UC)

## Customer meetings a success

Annual customer meetings offer a unique opportunity to discuss industry challenges with Elsevier MDL and industry colleagues, learn about MDL® solution strategies (and those of other vendors), see product demonstrations and even receive hands-on, intensive training on new products—always in a relaxed atmosphere with plenty of time for conversation and social interaction.

The theme of this year's European User Group Meeting (EUGM, held this March at the Hilton Prague Hotel) and US User Conference (US UC, held this May at the Paradise Valley Resort in Scottsdale, Arizona) was 'Integration of Information to Support Workflows and Decisions.' With concurrent Biology Data Management Exchanges, both gatherings attracted a good mix of IT, chemistry and biology customers from pharmaceutical and biotech companies of all sizes, and from academia.

At the EUGM, Ulrich Jordis of the Technical University, Vienna, spoke about information retrieval and use in academia with a focus on tools and techniques used daily in academic chemistry labs. Attendee Thibaud Viala, director general of Klee Group, an MDL® Isentris Alliance partner, said the EUGM was "definitely a place where one can feel future directions in drug discovery information systems."



*Keynote speakers at the US User Conference were Dr. Yvonne Martin of Abbott Labs and Dr. Tudor Oprea of the University of New Mexico.*



The keynote speakers at the US UC were Dr. Yvonne Martin, Abbott Laboratories, who spoke on information needs in modern discovery, and Dr. Tudor Oprea, University of New Mexico School of Medicine, who spoke on new cheminformatics techniques in drug discovery. Rich Lawson of AstraZeneca discussed the technical, organizational and behavioral issues involved in setting up and deploying enterprise information portals.

In a well-received scientific presentation, Mark Daly of the Broad Institute talked about the role of chemo-

and pharmacogenomics in opening up new approaches to therapy and drug discovery with a focus on how informatics is essential in supporting these new techniques. Stephen Michalec of Cephalon said: "It's been several years since my last user meeting. The content and social activities made this the best I have attended"

The social events at the European and U.S. meetings offered an interesting commentary on the contrasting styles of the two

locales. The EUGM Thank You dinner was held in an ornate, baroque chateau outside Prague. The US UC get-together was a hoedown on a dude ranch featuring Native American dancers, a cowboy gun-twirler and a buffalo-rider. ■

Mark your calendars for next year's  
European and U.S. gatherings!

**European User Group Meeting**  
March 6-8, 2006  
London

**US User Conference**  
May 7-11, 2006  
Jersey City, NJ

# Mark your calendars!

You can find Elsevier MDL at the following events over the next few months.

## DRUG DISCOVERY TECHNOLOGY® AND DEVELOPMENT WORLD CONGRESS

Boston, MA, August 9-11, Booths 901/1001

## FALL ACS NATIONAL MEETING

Washington, DC, August 28-September 1, Booth 1401

## JAPANESE USER GROUP MEETING

September 7-9

For information, contact Keiko Ogita ([k.ogita@mdl.com](mailto:k.ogita@mdl.com))

## SOCIETY FOR BIOMOLECULAR SCREENING (SBS)

Geneva, Switzerland, September 11-15, Booth 463

## DRUG DISCOVERY TO CLINICAL TRIALS

Mumbai, India, October 5-7

## ISSX/JSSX

Maui, Hawaii, October 23-27

## PACIFICHEM 2005

Honolulu, Hawaii, December 15-20

For more details, go to [www.mdl.com](http://www.mdl.com). Click on **Company Info** and **Events**.

### MDL® Isestris® & MDL® ISIS administration training now available

Elsevier MDL is pleased to announce the availability of public MDL Isestris and MDL ISIS administration training at an Elsevier MDL location near you. The following courses are available in both the United States and Europe:

**MDL® Base Administration**

**MDL® Core Interface Administration**

**MDL® Direct Administration**

**MDL Relational Chemical Gateway  
Administration**

**MDL® ISIS/Host Administration**

In addition, a sixth course, "**Hview Design, Development and Optimization**," is available in Europe only.

For course objectives, dates/locations, pricing and registration instructions, go to [www.mdl.com](http://www.mdl.com) and click on Education/Course Catalog.

For more information, contact Cypryan Klish at (510) 357-2222, ext. 1388 ([c.klish@mdl.com](mailto:c.klish@mdl.com)) in the U.S. or Elke Schneider-Locher at +41 61 486 8842 ([E.Schneider-Locher@mdl.com](mailto:E.Schneider-Locher@mdl.com)) in Europe.

### Elsevier MDL Web Workshops

Elsevier MDL offers the following two-hour, interactive Web Workshops for groups of up to eight participants:

**Exploring DiscoveryGate®**

**MDL® ISIS/Base 2.5: Inspecting  
Metabolic Outcomes and Adverse  
Toxic Effects**

**MDL® ISIS for Excel for the Current  
ISIS User**

**MDL® Report Manager: Creating  
Reports from MDL ISIS Databases**

**Transition to MDL® CrossFire®  
Commander 7.0**

**Using MDL CrossFire Commander 7.0**

**Searching CrossFire Beilstein using  
MDL CrossFire Commander**

For general information on Web Workshops including more detailed topic descriptions, contact Veronica Zuniga at [edservices@mdl.com](mailto:edservices@mdl.com) or 800-955-0051, extension 1326.

If you wish to sign up for a workshop (which can be limited to participants at individual sites) or to arrange custom workshops on topics of your own choosing, contact an Elsevier MDL account manager or Peg Renery at [p.renery@mdl.com](mailto:p.renery@mdl.com) or 800-955-0051, extension 1377.

For more information on Elsevier MDL training programs, click on Education at [www.mdl.com](http://www.mdl.com).



## *New tools to streamline discovery*



**Elsevier MDL is launching three new workflow solutions at Drug Discovery Technology® and Development in Boston, August 9-11.**

### **MDL® Logistics**

For finding, ordering and managing reagents in a coordinated workflow

### **MDL® Notebook**

The next-generation hub of your collaborative e-R&D environment

### **MDL® Assay Explorer® 3.0**

The biological data management system offers impressive performance and integration enhancements

*Come to booths 901/1001 to see how these products can improve your productivity.*



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