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AstraZeneca and MDL® Direct
Streamlining substructure searching

***The next generation in
chemistry registration***

A new domain service
within MDL® Isentris™

DiscoveryGateSM

Mining for drug leads

MDL® Plate Manager

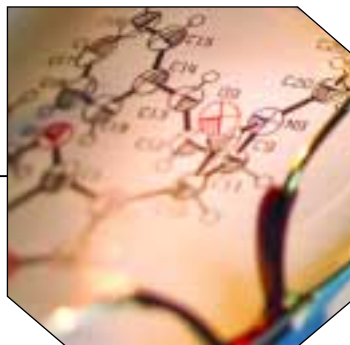
Simplifying sample management



MDL®

C M O L E C U L A R C O N N E C T I O N

2004 • Vol 22 No 1



3 ONE-ON-ONE

New approaches to meeting customer needs from Elsevier Life Sciences Business

4 CORPORATE CONNECTIONS

The MDL Scientific Advisory Board assesses the optimal use of computing power and integration in discovery informatics. • In the news • MDL GmbH donates CrossFire Beilstein and CrossFire Gmelin licenses to the St. Petersburg State Institute of Technology.

6 CUSTOMER CONNECTIONS

AstraZeneca builds a proprietary, structure-searchable database for requesting in-house compounds. The fast and easy-to-use system is accelerating compound selection.

7 DISCOVERY INSIGHTS

MDL's chemistry registration domain service: A new, configurable, and extensible middle-tier chemistry service built on MDL® Isentris™

8 AT THE BENCH

DiscoveryGateSM: Mining bioactivity and metabolism/toxicology databases for compounds that can be used to treat Alzheimer's disease

11 DISCOVERY UPDATES

An in-depth look at how DiscoveryGateSM saves researchers' time • Planning synthetic routes with DiscoveryGateSM • Simplifying sample management with MDL® Plate Manager • Improved registration and workflow integration with MDL® ChemBio AE 2.0 • Introducing MDL® Assay Explorer Visualizer: A new tool for viewing plate-based data • Customer-requested enhancements drive upgrades to latest MDL server products.

15 PARALLEL REACTIONS

Conferences, conventions, training courses, and other parallel activities for connecting with customers

World Headquarters
MDL Information Systems, Inc.
14600 Catalina Street
San Leandro, CA 94577
TEL: (510) 895-1313
FAX: (510) 483-4738
www.mdl.com

New Jersey
Morristown, NJ 07960
TEL: (973) 292-3684
(800) 401-4321
FAX: (973) 734-1792

Switzerland
MDL Information Systems AG
Allschwil, Switzerland
TEL: +41 61-486-88-88
FAX: +41 61-486-88-89

Cologne
TEL: +49 221-16025-255
FAX: +49 221-16025-68

Oslo
Authorized Agent Scandinavia
TEL: +47 22-44575-6
FAX: +47 22-43416-6

Sweden
TEL: +46 (0)46-2888630
FAX: +46 (0)46-129879

Paris
TEL: +33 1-45 36 80 00
FAX: +33 1-45 36 80 01

Frankfurt
MDL Information Systems GmbH
TEL: +49 69-5050 420
FAX: +49 69-5050 4245

United Kingdom
MDL Information Systems (UK)
Camberley, Surrey, U.K.
TEL: +44 (0)1276 701500
FAX: +44 (0)1276 701501

Japan
MDL Information Systems Japan K.K.
Tokyo, Japan
TEL: +81-3-3230-2641
FAX: +81-3-3230-2761

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Vice President Corporate Communications: Phil McHale
Editorial Staff: Harold Bradley and Erik Miller
Production Manager: Anne DeLaFiguariere
Design: Steve Naegele Design, Fremont, CA
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Bill Balke, Global Biopharma Business



Jean Colombel, Global Corporate Business

The formation of Elsevier Life Sciences gives customers a unified sales organization that offers MDL and Elsevier products and services through a single Account Manager. To better serve customers, the new organization features units dedicated to specific types of customer organizations. To illuminate these distinctions and elaborate on the new sales organization's relationship with customers, Molecular Connection interviewed Jean Colombel, vice president of Global Corporate Business and Bill Balke, vice president of Global Biopharma Business.

Bill Balke and Jean Colombel

The new Elsevier Life Sciences sales organization

What motivated the sales reorganization into corporate and biopharma accounts?

Jean: The motivating concept behind the new organization is to stay current with our customers and align with our customers' business goals. We've seen our largest customers putting organizations in place with global missions and global responsibility. Our new organization had to be responsive to the broad market developments impacting customers with worldwide operations.

Bill: Then there are the other companies—which may be large, but for all intents and purposes are centralized in one location. These companies are in the early stages of development, or in a more dynamic organizational state where they need rapid changes in services or products. This distinction in the market led us to the decision to structure the organization in terms of corporate and biopharma accounts.

How will a dedicated biopharma team help customers?

Bill: There's a lot of benefit to be derived when the people serving a market are intimately familiar with its particular needs. They can apply best practices information across the industry, leverage common software products, and avoid the common implementation pitfalls. It's been my experience that the difference between success and failure is based more upon the process of implementing the products than anything else. A successful project plan is one of the biggest keys to achieving success in a particular market.

I have always felt that emerging customers needed to have a spokesperson for the needs of this particular market. A number of people in the biopharma organization are uniquely qualified to speak to these needs. Paul Collins, the director of Biopharma in Europe, and Bob Olszewski, the Biopharma director in the Americas, are very

tuned to the situations of rapidly growing companies. They understand the challenges these companies face, their particular research requirements, and the resource restraints under which they're operating. They are comfortable putting together collections of products and services that meet the specific needs of biopharma companies.

What benefits will customers see from the unified Elsevier Life Sciences sales organization?

Jean: This new organization is really a merger of Elsevier people and MDL people.

It is two groups of experts coming together, with an opportunity to help customers take advantage of synergies between the product suites. The advantage of simplifying contacts goes beyond simplifying the process of making future investments for our customers; it really allows us to better understand the customer, their strategy, and where they would like to go with us. And the customer doesn't have to repeat the same story and have similar discussions with different Elsevier and MDL contacts.

How are customers responding to the changes?

Jean: We've gotten very good feedback from everyone we've spoken too. One customer said, 'This is exactly the way we are organized internally.' The key is the simplified relationship. Customers don't have to spend time deciphering the architecture of the relationship. They expect us to be aligned with their processes.

Bill: There is very good resonance with our customers. They feel that this is something that will give them a better voice in the development of new MDL products—they see that there is a

(continued on page 5)

Scientific Advisory Board addresses computing and integration

The second very successful and productive meeting of the MDL Scientific Advisory Board (SAB) took place amidst the red rock splendor of Sedona, Arizona in November. This was the first opportunity for the SAB to get to know new MDL CEO Bernard Aleva, and for Elsevier Life Sciences Managing Director Martin Tanke to present the Elsevier vision and strategy.

Building on the first SAB meeting held in California in February 2003, the SAB members and MDL and Elsevier participants focused their attention on three main areas of strategic importance to our customers: the optimal use of computing power and informatics in discovery; the need for and value of data and information integration; and the best ways to integrate and interlink the large amounts of scientific, technical, and medical (STM) information available from Elsevier to enable scientists to answer pressing, but as-yet difficult or impossible-to-ask questions.

The SAB identified several key areas where the application of computing power can enhance discovery. They discussed predictive tools (stressing the importance of appropriate validation), workflow management tools, including electronic lab notebooks, and project/portfolio management tools. Data and information integration were seen as necessary but not as a panacea, and the SAB felt that the true value of integration would be realized through the applications which integration would enable.

Elsevier has a broad and expanding STM content portfolio (e.g., DiscoveryGateSM, ScienceDirect[®], EMBASE.com, xPharm, etc.), and the SAB stressed the need for chemists and biologists to be able to explore this vast repository together—combining structure and text/sequence searching; linking expression

data, functional biology, and structure; and mining disease pathways.

SAB participants at the meeting were Helen Berman (Rutgers and Protein Data Bank), Jim Golden (CHI Insights), Joe Guiles (Replidyne), Sangtae Kim (Purdue), Hugo Kubinyi (BASF, retired), Irwin "Tack" Kuntz (UCSF), Jim Summers (Abbott), and Alex Tropsha (UNC). MDL and Elsevier staff in attendance were Martin Tanke (Managing Director, Elsevier Life Sciences), Bernard Aleva (CEO), Lars Barfod (CBO), Seth Pinsky (CTO), Kevin Cannon (VP Marketing), Doug Hounshell (VP Content Development), and Phil McHale (VP Corporate Communications and Scientific Affairs). ■



In the news

BASF Aktiengesellschaft, the world's leading chemical company, has adopted the new MDL[®] Isentris[™] technology to improve its global information management tools in research and development. The agreement includes MDL[®] Core Interface, a middle-tier server that integrates key services for managing discovery data; MDL[®] Draw, a first-of-a-kind chemical drawing application that allows researchers to draw and edit chemical compounds; and MDL[®] Direct, data cartridge technology for searching molecules and reactions stored directly in Oracle[®] databases.

Organon, the largest Dutch pharmaceutical company, has signed an agreement with MDL to update its R&D information infrastructure with MDL[®] Direct data cartridge technology. MDL Direct makes structures stored in Oracle[®] databases accessible to research scientists and developers. The data cartridge technology enables Organon to manage fully relational molecule structure databases while integrating other corporate data in an open Oracle environment.

VWR International Inc., a leading global laboratory supply distributor, has teamed with MDL in a joint effort to provide mutual customers with timely access to accurate information for chemical sourcing. The companies' agreement to exchange electronic catalog data will simplify the updating of MDL[®] Available Chemicals Directory and offer streamlined chemical ordering to customers that use www.vwr.com to place an order. ■

CrossFire Beilstein comes home



Friedrich Konrad Beilstein

Scientists in St. Petersburg, Russia had a lot to celebrate in 2003—the 300th anniversary of the city, the 175th anniversary of the St. Petersburg State Institute of Technology, and (for those with an interest in chemistry) the 165th anniversary of the birth of Friedrich Konrad Beilstein (1838-1906), the originator of the celebrated *Beilstein Handbook of Organic Chemistry*.

Beilstein was the head of the Chemical Laboratory at the St. Petersburg State Institute of Technology, then the Imperial Technical Institute, for 30 years, from 1866 to 1896. When he first published his Handbook in 1881-83, it was a 2-volume, 2,200-page compendium of around 15,000 compounds, and it was written in German. Today it is an electronic compilation, in English, of approximately 8.5 million compounds and the world's largest chemical facts database. MDL Information Systems GmbH licenses and markets the current system as CrossFire Beilstein.

"What differentiates Beilstein's encyclopedia of organic compounds from other collections is its triangular interlinking of molecular structure diagrams, characteristic chemical properties, and preparative methods," says Dr. Alexander J. Lawson, director of R&D at MDL Information Systems GmbH. "The rules Beilstein established in 1881 for determining admissible entries are still rigorously followed today. Only properly validated and cited chemical structure and property data make it into Beilstein."

Founded in 1828, the St. Petersburg State Institute of Technology is one of the oldest and most renowned chemical education establishments in the world. To commemorate the Institute's jubilee celebration and our shared interest in the Beilstein data, MDL GmbH has donated special three-year CrossFire Beilstein and CrossFire Gmelin licenses to the Institute, enabling academic researchers there to search, view, and print chemical structures and data for internal research and educational purposes. As the world's largest collection of inorganic and organometallic compounds, CrossFire Gmelin complements CrossFire Beilstein as an indispensable tool for researchers designing new materials and catalysts.

Dr. Anatoly S. Dudyrev, rector of the State Institute of Technology, says: "The Beilstein data are an invaluable, timeless resource for chemists. Although Beilstein introduced his *Handbook* right here in St. Petersburg, the library of the State Institute of Technology has never possessed today's modern electronic resource. Thanks to MDL, this wealth of chemical knowledge is now available, where it originated, in a convenient, easy-to-use software system."

Prof. Dudyrev has agreed to organize and host regular symposia at the State Institute of Technology. These events will feature lectures on the Beilstein database, search system, and derived electronic information, as well as demonstrations of CrossFire Beilstein and other MDL solutions. ■

(continued from page 3)

path to the decision-making process. For a number of years some biotechnology and biopharma companies have felt that their business was not important to MDL because they were such small fish compared to the larger global pharma companies. I think that a number of the companies feel this [reorganization] is a recognition on the part of MDL that the emerging biotechnology and non-traditional customers have achieved a level of success and respect that is deserving of having their own representation in the marketplace.

How will the combined Elsevier portfolio support customers?

Jean: People are looking for more unified and integrated tools for information. Elsevier is the

leader in publishing and MDL the leader in informatics. So providing the two together demonstrates our commitment to integrated content and workflow applications—a total solution. It's important to stress, and I believe customers realize and are intrigued by this, that we are not just integrating products for the sake of introducing integration, but we are really trying to partner with our customers to deliver the most relevant solutions to important research challenges; solutions that deliver extensive internal and external content in a unified value-added manner. Customers want to simplify and reduce the number of interfaces that scientists have to use. That's a shared goal: we're working for the benefit of developers and scientists.

Bill: There are a large number of Elsevier customers that do not currently have MDL

products and have not been exposed to MDL products and services. Likewise there are customers of MDL products and services that have not taken advantage of (at least on a corporate level) subscriptions to Elsevier publications or other Elsevier products such as EMBASE™, BioTechSelect, or the Mouse Knockout Database, simply because they aren't aware of the availability of these products. Now that we're bringing to customers the full benefits of Elsevier Life Sciences' expanded product mix, we'll be engaging with them earlier in the process, before they've traditionally needed MDL chemistry and screening biology products. As a result, I think we'll have a longer-term relationship with customers and be better able to partner with them in accelerating innovative and successful scientific research. ■

ONE-ON-ONE

AstraZeneca accelerates substructure searching with MDL[®] Direct

“A search that returned 11 hits—that’s 11 molecules out of 5.5 million—took only three seconds. [Such] searches are just blazingly fast from our point of view.”

Mark Duffield, principal informatics scientist, AstraZeneca Pharmaceuticals

One of the world's top five pharmaceutical companies, AstraZeneca is a leading provider of gastrointestinal, oncology, anesthesia, cardiovascular, neuroscience, and respiratory products. With approximately 11,000 researchers worldwide and an annual research budget of over \$3 billion, the company's R&D pipeline is recognized as one of the best in the industry. To maintain its industry leadership, AstraZeneca's informatics specialists are constantly assessing new, cutting-edge technologies to manage the huge number of leads generated in the company's ongoing search for life-saving medicines.

Mark Duffield, principal informatics scientist at AstraZeneca's R&D facility in Waltham, Massachusetts is leading a team of computational chemists and software engineers that is using MDL[®] Direct to build a proprietary, structure-searchable database for requesting in-house compounds. Part of the MDL n-tier Isentris[™] discovery informatics architecture, MDL Direct is a cartridge-based data repository that manages chemical registration and searching in fully relational molecule and reaction databases. The proprietary database Mark is building currently contains approximately 5.5 million drug-like molecules, all of which have been filtered, processed, and standardized prior to registration. Mark expects the database to grow to 13 million structures and to continue expanding over the long term.

As a cheminformatics specialist, Mark manages software development projects supporting medicinal chemists engaged in lead generation and optimization efforts all the way through to candidate selection. The compound-selection database he is building with MDL Direct satisfies medicinal chemists' key requirements in the following areas:

- It is easy to use with no specialist training required. A medicinal chemist familiar with an MDL[®] ISIS/Base user interface can perform structure searches without the time-consuming assistance of a computational chemist.
- The database stores properties directly with structures, enabling chemists to filter by both parameters.
- Database searches are fast enough to accommodate practical discovery workflows.
- The use of MDL[®] Direct allows this application to be closely integrated with other AstraZeneca-owned proprietary systems.

When AstraZeneca began the process of choosing the best technology to implement this application, Mark and his team built a small trial database using an older version of MDL Direct and found that to be adequate for their needs. During AstraZeneca's implementation phase of the project, MDL made a newer version of this database product available, which has proven to be even more reliable. Using common substructure searches to benchmark database performance, Mark and his colleagues have observed impressive search speeds with MDL Direct.

“When I ran a search that returned approximately 196,000 hits, that search took only 20 seconds,” said Mark. “A more restrictive search that returned 11 hits—that’s 11 structures out of 5.5 million—took only three seconds. These searches are just blazingly fast from our point of view.”

This impressive search performance combined with the way an AstraZeneca-owned proprietary database is structured (i.e., putting all the structure and property information that chemists want to search on into the main part of the database)—and its ease of use—mean that a medicinal chemist can now single-handedly reduce 5.5 million structures down to the 20 to 40 of interest in under five minutes. The major time saving here is not so much in the search performance, however, but in the fact that the bench chemist can now handle this operation alone, without the assistance of a computational chemist. Previous systems used at AstraZeneca, prior to the company's merger in 1999, were not searchable by the chemists; more computer-savvy intermediaries were required to run the searches for them.

“By putting this search capability directly into the hands of the people who need it, we've turned a ‘days-or-weeks’ type of process into a matter of minutes,” said Mark. “The computational chemists get their time back, and the bench chemists quickly acquire the compounds they need to move on with their own discovery research.”

Approximately 30 researchers across AstraZeneca's global R&D organization are already using the new database in a pilot program. By changing the compound selection process from a day-long job requiring the intervention of a specialist to a 30-minute job that the average bench chemist can handle, MDL Direct is helping to streamline AstraZeneca's world-leading research efforts. ■



AstraZeneca R&D Boston

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MDL's chemistry registration domain service

The next generation in chemistry registration

“MDL's middle-tier technology is a solid environment for building a variety of services used by applications.”

Cindy James, MDL Project and Process Management

Chemical registration is the first essential informatics step in any discovery process involving small molecules.

A sophisticated set of business rules controls how structures and data are registered, how they are searched, and how information is managed at higher levels. The n-tier MDL® ISENTRIS™ discovery informatics platform provides the foundation for a new generation of registration systems in which business rules are managed in a middle tier capable of hosting a variety of new domain objects and services. Leveraging its unmatched industry experience, which includes the pioneering of advanced corporate chemistry registration systems for over 20 years, MDL has built and is successfully implementing a new registration service that is producing strong customer interest.

MDL ISENTRIS—a modern informatics technology that is extensible to support current and future industry requirements—is also the platform on which MDL has constructed a new chemistry registration domain service that provides:

- A standardized registration capability that can be reused across multiple applications (e.g., traditional single compound registration, electronic laboratory notebooks, parallel and combinatorial synthesis systems, externally purchased libraries, etc.)
- Extensibility to accommodate virtually any registration application and database with many user-configurable options
- The ability to easily handle compounds that cannot be described as a single “structure” (e.g., mixtures, formulations, and structure alternatives¹)

Chemistry registration applications and services

In a typical registration process, a scientist enters structures and data into a registration application, and the software automatically applies the appropriate business rules, performs a uniqueness evaluation, assigns structure/batch ID based on uniqueness, inserts structure/batch data, associates IDs with non-structural data, inserts non-structural data, and returns the results of the processing.

The registration application software that implements this process follows a user-defined workflow to enter chemical structures and associated data into multiple tables in accordance with corporate business rules. The registration application includes functionality for drawing structures, querying data, and browsing results, using existing MDL products such as MDL® Draw, MDL® Direct (data cartridges), MDL® Core Interface, and additional focused services such as the new chemistry registration domain service, which extends the middle-tier framework of MDL Core Interface.

“MDL's middle-tier technology is a solid environment for building a variety of services used by applications,” says Cindy James of Project and Process Management who is managing the project through its first iterations. “For example, MDL's new chemistry registration domain service consists of server-side software that evaluates a finite data set—a structure, a compound, or batch sample—based on established business rules governing structure normalization and uniqueness. If the data are accepted, they go into a predefined database structure. Programmers using this new domain service appreciate its open API, as well as its configurability and extensibility to fit in virtually any registration application and database.”

A flexible, multi-functional registration service

The chemistry registration domain service works together with MDL Core Interface to provide sophisticated business logic and a common application programming interface for inserting structure-based discovery data into a predefined database. The service manages compound and batch objects independently in accordance with established business processes, automating the generation of compound and batch IDs. Structure normalization and novelty check tools apply the business rules for determining structure uniqueness.

The functionality of the chemistry registration domain service is constantly evolving to provide the flexibility required by MDL customers. In the first iterations, the service includes the following customer-requested functionality:

- Accepts single or multiple batches via API or file
- Supports both synchronous and asynchronous registration
- Interfaces with MDL® Cheshire scripts or Cheminformatics Business Rules Manager (CBRM)
- Executes MDL Cheshire scripts for structure normalization
- Performs duplicate/uniqueness check on normalized structures
- Returns a corporate ID for each compound and a batch ID for each batch
- Inserts both structures and data into the chemical registration database
- Returns messages (status, error, warnings, Cheshire, etc.)

(continued on page 10)

¹ An example of a structure alternative would be two reactions, each yielding a separation of a mixture (of diastereomers or enantiomers). The result is two samples characterized by structure A or B, which are difficult to distinguish without additional analysis or experiments. Both need to be registered and both should get different compound IDs. The database structure of the chemistry registration domain service is capable of distinguishing between compounds characterized by the same “A or B” structure.

Mining DiscoveryGateSM

MDL[®] Compound Locator and **MDL[®] Database Browser** are complementary Web-based searching and browsing applications on DiscoveryGateSM.

MDL Compound Locator enables a researcher to survey MDL and third-party molecule and reaction databases for available information on compounds. It provides a general index or road map to information.

MDL Database Browser enables a researcher to search for compound or reaction information in a specific MDL database using structure, reaction, or data query parameters.

| | Structure | Pharmacological | Toxicity | Metabolism |
|---|-----------|--|---|----------------------------|
| 1 | | All sources Beilstein CCR CMC DWPI MDDR | Beilstein | Metabolite |
| 2 | | All sources Beilstein CCR CMC DWPI Index_Chemicus MDDR Metabolite Toxicity | All sources Beilstein OHS MSDS Toxicity | Metabolite |

Figure 1. Viewing the initial hit list from CMC in MDL Compound Locator reveals the occurrence of the retrieved compounds in the other underlying DiscoveryGate content sources.

DiscoveryGateSM is a powerful Web-based discovery environment that integrates, indexes, and links scientific information to give a researcher immediate access to compounds and related data, reactions, original journal articles and patents, and authoritative reference works on synthetic methodologies—all from a single entry point.

Consider a small biotech company that has developed an array of bioassays to evaluate drug effects within memory and cognition pathways. A researcher is interested in finding nootropic compounds (“cognition enhancers”) that can be used to treat Alzheimer’s disease—a condition recently labeled “epidemic” by one of the world’s leading dementia researchers, Professor Ashley Bush of Harvard Medical School and the University of Melbourne.

How can this researcher exploit DiscoveryGate to find compounds with the therapeutic activity of interest, then organize these

Substance

| | | | | | |
|--------------------------|--------------------------|-------------------|-------------|---|---|
| <input type="checkbox"/> | Activity | Contains | cholinergic | Delete Duplicate Info | |
| OR | <input type="checkbox"/> | Activity | Contains | cholinesterase | Delete Duplicate Info |
| NOT | <input type="checkbox"/> | Activity | Contains | Cognition Disorders, Agent for | Delete Duplicate Info |
| AND | <input type="checkbox"/> | Development Phase | Contains | Biological Testing | Delete Duplicate Info |
| OR | <input type="checkbox"/> | Development Phase | Contains | Preclinical | Delete Duplicate Info |
| OR | <input type="checkbox"/> | Development Phase | Contains | Discontinued | Delete Duplicate Info |
| OR | <input type="checkbox"/> | Development Phase | Contains | Withdrawn | Delete Duplicate Info |

[start search](#)

Search results 1 to 12 of 144

[View in MDL Compound Locator](#) [Set Sort](#)

Pages: [1](#) [2](#) [3](#) [4](#) [5](#) [6](#) [7](#) [8](#) [9](#) [10](#) [Next 10](#) [NEXT PAGE](#)

| | | |
|-----------------------------|-----------------------------|-----------------------------|
| Details | Details | Details |
| Details | Details | Details |
| Details | Details | Details |

Figure 2. Searching MDL Drug Data Report for cholinesterase inhibitors that are not reported cognitive enhancers and have not reached clinical trials produces a list of 144 lead compounds.

for drug leads

compounds according to structural class, expand the search to encompass known preclinical development compounds that might exhibit the same activity, examine associated toxic properties and metabolic pathways, and identify companies with promising early-stage drug candidates against proven targets?

The starting point is Comprehensive Medicinal Chemistry (CMC), a specialized database of 8,500 pharmaceutical compounds with known therapeutic activity. Using MDL® Database Browser's intuitive interface to search CMC for "substance class" containing the string "anti-Alzheimer" returns a list of 17 compounds that are classified as cognitive enhancers and, in some cases, as cholinergic or cholinesterase inhibitors. Having retrieved a set of relevant results from CMC, the researcher can gain a broader perspective by transferring the list to MDL® Compound Locator and searching over the Compound Index (refer to Figure 1). The Compound Index provides a view of over 12 million compounds found in MDL and third-party databases. For example, 10 of the 17 compounds are registered in the Derwent World Patents Index (DWPI), and 7 of these 10 specify that they are acetylcholinesterase inhibitors intended for oral compositions useful in treating amyloid disease, e.g. Alzheimer's disease.

To look for possible new lead compounds, the researcher can now use MDL Database Browser to open MDL® Drug Data Report

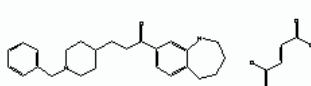
| Structure | Pharmacological | ⊕ Toxicity |
|---|--|--|
|  | All sources Beilstein DWPI MDDR | All sources Beilstein MDDR Toxicity |

Figure 3. The first lead compound on the list is registered to several databases.

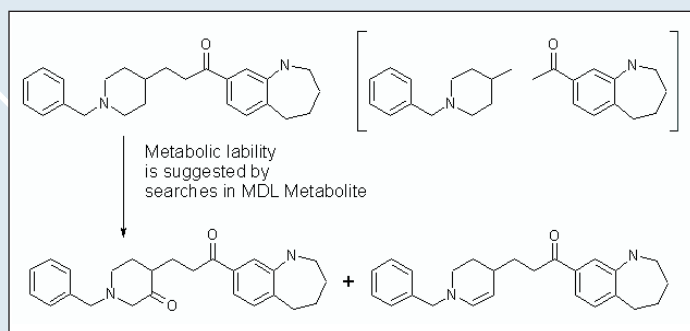


Figure 4. Although the structure itself is not registered to the MDL® Metabolite Database, an intuitively reasonable one-bond deconstruction produces two fragments. A simple substructure search reveals the likely biotransformations shown.

(MDDR), a database of over 140,000 drug development compounds. Here the scientist can conduct a search for cholinesterase inhibitors that are not reported cognitive enhancers and that have not reached clinical trials for other therapeutic purposes. This produces a list of 144 lead compounds that have the desired enzyme inhibition and which, by inspection of the list, are not structural analogs of the known anti-Alzheimer's agents (refer to Figure 2).

Returning to Compound Locator, the researcher finds direct hyperlinks to relevant data as shown in Figure 3.

The researcher can drill down to additional information on pharmacology and toxicity from CrossFire Beilstein and MDL® Toxicity Database or view patent information in the Derwent database. A quick additional step makes it possible to draw conclusions about the likely metabolism of this compound as shown in Figure 4.

Even a casual look at the list shown in Figure 3 suggests that these 144 compounds may be grouped based on structural similarity, and the 'Organize Results' feature in Compound Locator generates such clusters automatically (Figure 5). The researcher can use generic structures representing these clusters to expand the original list of 144 compounds. Referring to Figure 5, a simple substructure search over the Compound Index using I as the substructure query elicits 72 structures in addition to the 18 found in MDL Drug Data Report. Substructure searches with II and III find, respectively, 435 and 161 additional examples from these compound classes. Thus, the researcher has expanded the original three clusters containing 54 compounds to encompass 722 known compounds.

Using DiscoveryGate researchers can pose single queries against vast amounts of data to find content relationships and then drill down into any of the sources for details, seamlessly linking from references to original articles using MDL® LitLink. Since MDL maintains the software/hardware and handles all security/database upgrades, the DiscoveryGate platform saves research organizations the time and expense of maintaining a search engine and updating content. Companies can quickly deploy DiscoveryGate to all their chemists, empowering them to focus on the scientific research that is their proper pursuit.

For more information on mining DiscoveryGate for lead compounds, visit www.discoverygate.com, or contact your local MDL Account Manager. ■

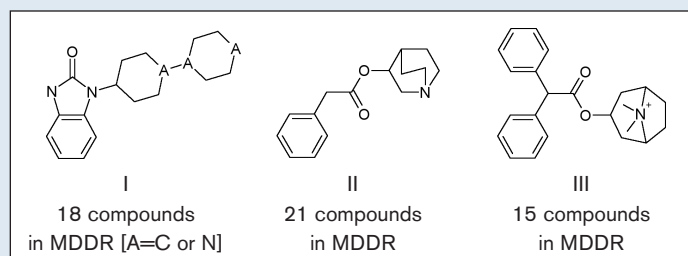


Figure 5. The three largest clusters produced by the Organize Results feature in Compound Locator include compounds represented by these generic structures which may be used as queries to develop large lists of possible lead compounds.

(continued from page 7)

Expanding middle-tier chemistry services

MDL has observed a strong market demand for additional middle-tier services similar to the chemistry registration domain service. All the attributes of a modern informatics technology like MDL Isentris—openness, flexibility, scalability, and extensibility—are driving the development of chemical warehouse, calculation, combichem, experiment management, procurement, and literature services, to name but a few.

Aleksandar Ruzicic of Global Biopharma Solutions says, “MDL will standardize other middle-tier services to provide essential business logic to MDL customers. In the context of a registration solution, MDL has already built an enumeration domain service based on MDL Cheshire for chemists performing parallel or combinatorial chemistry experiments. Another area MDL is currently exploring is an experiment management service that optionally includes the ability to register reactions.”

Charles Buse, Ph.D., of Solution Design and Implementation and the scientific and technical leader of the project, observes, “The new chemistry registration domain service, maintained and supported by MDL, provides a robust, server-side foundation for any corporate registration application. In addition, it will effectively support any related workflow application that requires compound/batch registration into a corporate database—including an electronic laboratory notebook application.”

Towards a viable chemistry electronic laboratory notebook

A corporate chemistry registration application, usually centered around compound and batch information, is the cornerstone of most chemical

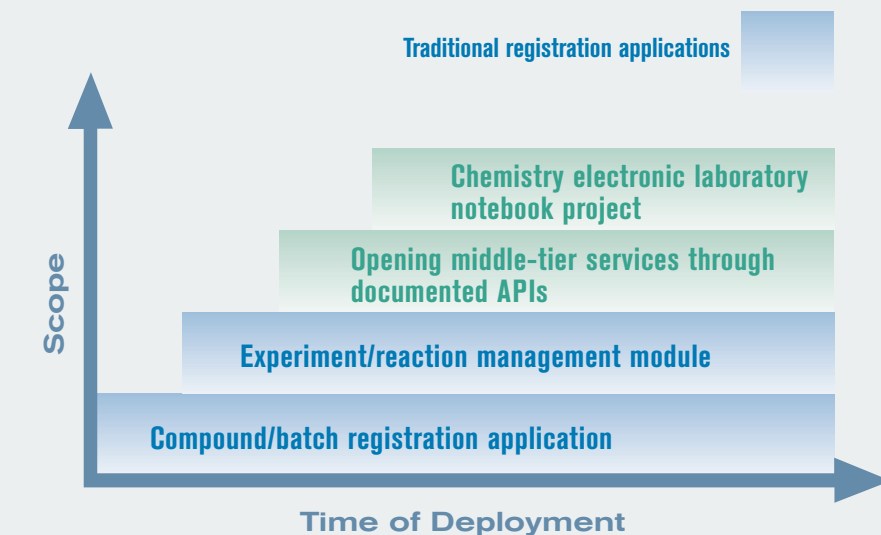


Figure 1. Compound/batch registration and experiment/reaction management capabilities are the cornerstone of chemical R&D. By opening middle-tier services through documented APIs, organizations can extend these capabilities to encompass compound sourcing, logistics, electronic notebook, and other applications.

R&D activities. Organizations may subsequently add components to extend the capabilities of these applications to manage experiments and reactions. When considering the introduction of chemistry electronic laboratory notebooks, organizations should investigate how they can best tap into the functionality of these existing application components.

Mario Dimayuga, Ph.D., of Global Corporate Solutions stresses that the most effective way to do this is to redesign registration applications following the n-tier architecture paradigm. With reference to Figure 1, Dimayuga asserts that R&D organizations need to “expose the specific business logic for reuse by opening its underlying functionality as middle-tier services

and making these services available through documented and accessible APIs.” Dimayuga continues: “This serves as the distinct mechanism through which all registrations are processed. This applies not only to electronic notebooks, but also to compound sourcing and logistics applications. Without this single mechanism, scientists would be able to enter compound/batch information into the corporate database through various unregulated mechanisms, making it impossible to maintain a reliable and coherent corporate chemistry database.”

A White Paper on the chemistry registration domain service is available from your Account Manager, who can also put you in touch with an MDL expert for further discussions. ■

DiscoveryGateSM:

When time is of the essence

Time is a precious commodity, especially for life science researchers who are synthesizing and testing large numbers of compounds to select and optimize the most promising leads. As a scientist, you want to spend more time exploring the most relevant data and generating creative hypotheses. You want to spend less time opening and closing applications, memorizing passwords, and mastering assorted login procedures.

By consolidating and integrating information access that previously required multiple applications and complex, often overlapping resources, DiscoveryGateSM dramatically simplifies and streamlines research tasks. In one workflow study, DiscoveryGate achieved 75% time savings over individual database searches conducted using multiple browsers.

Log in once and begin exploring

A single login to DiscoveryGate gives you access to a normalized pool of more than 12 million structures and over 200 million associated facts from databases offered by MDL including MDL[®] Available Chemicals Directory, MDL[®] Drug Data Report (developed in collaboration with Prous Science), and CrossFire Beilstein, as well as from indexed third-party sources such as Thomson Derwent's World Patents Index[®] and Thomson ISI's Current Chemical Reactions and Index Chemicus[®] (appropriate subscriptions and licenses required to access third-party content in their environments). The wealth of information available on DiscoveryGate is accessible from one location, requiring only one username/password.

Access structures and data with a single query

Different data sources employ different chemical structure drawing conventions. DiscoveryGate normalizes these diverse

representations using the MDL[®] Cheshire interface. As a result, a single structure-based search across multiple databases produces a roadmap showing you which databases contain information relevant to your hit set, regardless of whether you have access to the databases or not. You don't even need to know which databases are likely candidates. Simply submit your query and let the system tell you where to find the most pertinent information.

Perform structure-based calculations


Because DiscoveryGate's normalized structure pool includes calculated properties, you can insert structure-based calculations as either search criteria in a query or as sort criteria when viewing results. Available calculations include Number of Proton Acceptors (O+N), Number of Proton Donors, calculated logP, torsional degree of freedom, and molecular weight of largest molecule fragment.

Quickly acquire a summary view of relevant data

DiscoveryGate provides a valuable summary view of relevant data (assuming appropriate access rights). This is a time saving feature because it rapidly consolidates relevant data culled from diverse and disparate data sources. For example, the system can consolidate pertinent data from CrossFire Beilstein, MDL[®] Drug Data Report, MDL[®] Comprehensive Medicinal Chemistry, and Index Chemicus in a single report—without requiring you to open separate databases, log in multiple times, formulate multiple queries, and reconcile multiple diverse result sets.

Generate standardized reports

The Summary View enables you to print a single, standardized report compiling information from multiple data sources. For example, you can view the calculated logP, a measured logP, a reported LD50 or IC50, as well as pharmacological and toxicological

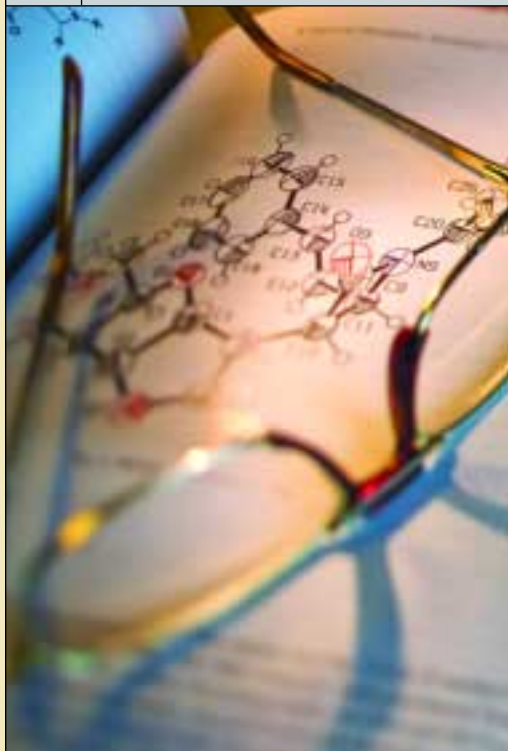


effects in context of the topology of a chemical structure. You can then group structures based on the pattern of availability of information or cluster compounds based on their structural properties to more effectively compare and assess targeted hit sets and promising leads.

Easily transfer results among applications

DiscoveryGate's Hop-Into and reaction linking functionalities streamline research by making it possible to transfer results easily among different applications. This means you can take full advantage of applications that are familiar to you and that provide the functionality you need. For example, you can use an interesting reaction found when searching for a reaction methodology as a query in Integrated Major Reference Works[™]. With a single click, you can explore the scope and limitations of the reaction.

For more information on how DiscoveryGate can save time and accelerate research at your organization, contact your local MDL Account Manager or visit www.discoverygate.com. ■



Organic chemists developing synthetic routes to target molecules must typically consult multiple sources of reaction information, including journals, patents, various reaction databases, and major reference works in organic chemistry. The process of locating this information can be time-consuming and difficult, especially if only hardcopy sources are accessible, if the information is only partially available electronically, or if the electronic sources are not integrated.

DiscoveryGateSM from MDL puts comprehensive, integrated information for synthesis planning at your fingertips, enabling you to access structure, reaction, and associated data, journal articles and patents, and major reference works on synthetic methodologies—all from a single entry point.

CrossFire Beilstein includes over nine million reactions, which are useful in the preparation of starting materials and key intermediates for a synthetic plan. With over one million reactions focused on new synthetic methods and an emphasis on substituent effects, ChemInform Reaction Library is an excellent resource supporting the design of novel compounds for target molecules. Other specialty databases include MDL[®] Reference Library of Synthetic Methodology for historical reactions, Derwent Journal of Synthetic Methods for current literature, including patents, MDL[®] Solid-Phase Organic Reactions for information on organic synthesis on solid-

DiscoveryGateSM: All the tools for complete synthesis planning— in one place

support, and Organic Syntheses for proven methods of preparations of organic molecules. The ability to search all of these key sources concurrently ensures that you do not miss valuable information.

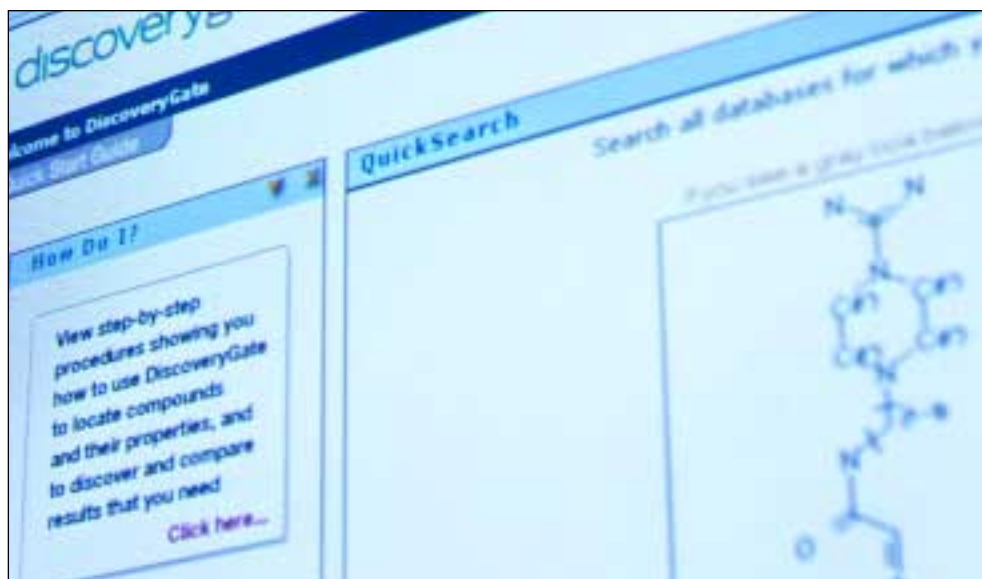
Once you've found a key reaction in a database search, you'll typically look for more information about the scope and limitations of that reaction to determine the suitability for synthesis of a new compound. In DiscoveryGate, you can immediately link from a reaction in a database to associated information about similar reactions in one or all of the following major reference works: Elsevier's *Comprehensive Organic Functional Group Transformations*, Springer-Verlag's *Comprehensive Asymmetric Catalysis*, John Wiley & Sons' *Encyclopedia of Reagents for Organic Synthesis*, and Thieme's *Science of Synthesis*. As with the databases, it is often useful to examine several of these complementary references to obtain the most comprehensive information.

Conversely, you may conduct structure, reaction, or text searches over the reference works to gain a general idea of the usefulness of a specific synthetic methodology. Then you can link directly from a given reaction in a reference work to similar reactions in one or more of the reaction databases to see how other researchers have used the same methodology.¹

By enabling you to search many data sources at once, DiscoveryGate rapidly provides a more complete picture of the reaction information available to solve a synthetic problem or plan a suitable synthetic route. DiscoveryGate also greatly reduces the time it takes to gather information when querying data sources separately.

For more information on how DiscoveryGate can speed up synthesis planning in your research lab, visit MDL's synthesis solutions Web site at www.mdl.com/promos/synthetic.methodology. ■

¹ All citations in all of the databases and major reference works are linked to the original electronic publication, if available, via MDL[®] LitLink.

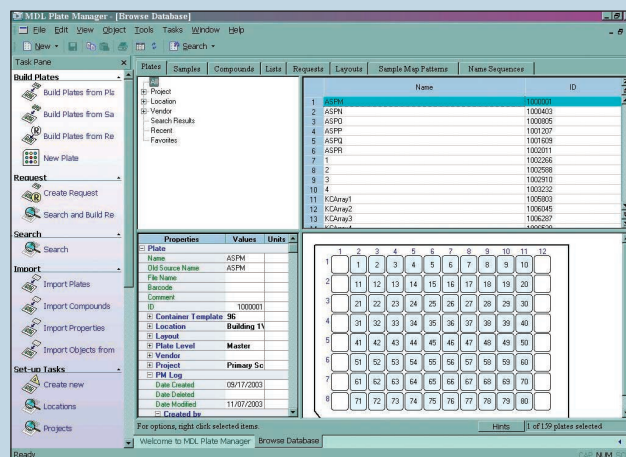


MDL® Plate Manager—Simplifying and streamlining sample management

MDL® Plate Manager makes it easy for researchers to locate samples, request plates, and track sample history, volumes, and freeze/thaw cycles. By resolving supply chain bottlenecks, ensuring sample integrity, and reducing cycle times, MDL Plate Manager helps customers identify higher quality leads faster and more efficiently, saving time and money while accelerating discovery workflows.

MDL Plate Manager is built on MDL® Isentris™—the modern, scalable, industry-standard architecture that enables the rapid development and deployment of integrated applications for drug researchers.

Using MDL Plate Manager, researchers can easily build and reformat plates, making master, daughter, dilution series, pooled samples, and cherry-picked plates. Powerful data visualization capabilities enable researchers to view multiple sample properties in plate layouts and then drill down to view relevant structure and batch details. With sample data, including plate availability, securely stored in a central database, inventory scientists can quickly determine what inventory is available and what needs to be replenished. Plates are created as needed, avoiding duplicate inventory and depletion of valuable compound stock. A request queue helps scientists anticipate material demand, prioritize orders, and predict workflows, thereby shortening plate fulfillment cycles. By enabling scientists to monitor and limit the number of freeze/thaw cycles, MDL Plate Manager helps inventory scientists maintain high-quality compound libraries, reducing expensive and time-consuming assay retests.



MDL® Plate Manager's database view enables scientists to select plates and samples quickly for replication or cherry picking. The system also tracks freeze/thaw cycles and automatically decrements volumes permitting organizations to track libraries efficiently and better ensure the quality of screened compounds.

MDL Plate Manager is fully integrated with data management and chemical registration tools, including MDL® ChemBio AE and MDL® Assay Explorer®. The open API enables customization and integration with lab automation and third-party software. For details on how this new sample/plate management solution supports more efficient, cost-effective lead generation, contact your local MDL Account Manager or submit a request for information at www.mdl.com. ■

MDL® ChemBio AE 2.1—More support, better workflow integration, and easier registration

For companies seeking a cost-effective solution for chemical registration and for the retrieval and viewing of chemical and biological data side by side, the new release of MDL® ChemBio AE is easier to use and more practical than ever.

MDL ChemBio AE 2.1 offers enhanced features, integration with key biology workflow applications MDL® Assay Explorer and MDL® Plate Manager, and greater compatibility with standard Oracle®, Microsoft®, and Sun environments, making it an ideal out-of-the-box registration and storage system.

Scientists have the power to register single compounds or entire libraries with ChemBio AE configured to check for duplicates, strip salts and solvents, assign ID numbers, and calculate chemical properties. ChemBio AE significantly speeds the registration process compared to manual registration, and a powerful library loading process increases the speed with

which compounds are available for biological testing. Integration with biological and logistics systems increases efficiency and data interpretation, enabling faster lead identification.

Now, improvements in ChemBio AE include faster search performance, customizable fields, an enhanced user interface for easier registration including additional drop-down lists, and improved ability to track analytical test data and handle solubility and addends.

With support for Oracle9i™, Microsoft® Windows 2000 and 2003, and Sun Solaris™ 8 platforms, the new release gives companies more options for adopting ChemBio AE. And the new release supports MDL® ISIS/Host 5.0, MDL® ISIS/Desktop 2.5, and MDL® Cheshire 3.0 with the latest in stereochemistry representation conventions.

Support for MDL Assay Explorer 2.2 and integration with MDL Plate Manager 2.0 makes it easy for organizations to support their research

workflows. Integration with Assay Explorer allows biologists and chemists to share information easily on lead candidates and assay results. Structures and compound data stored in ChemBio AE are accessible via Assay Explorer, and the *in vitro* and *in vivo* biological assay results for a compound are in turn searchable and viewable in ChemBio AE.

The integration between ChemBio AE and Plate Manager dramatically simplifies the process of creating and formatting plates from purchased libraries. During the registration of library SDFs, the crucial information needed by Plate Manager is registered into the ChemBio AE database, and readily supplied to Plate Manager. And, since ChemBio AE serves as the central structure repository, maintenance of the corporate structure database is centralized.

MDL ChemBio AE 2.1 is available now. For more information visit www.mdl.com or contact an MDL Account Manager. ■

MDL[®] Assay Explorer Visualizer—A new tool for analyzing plate-based data

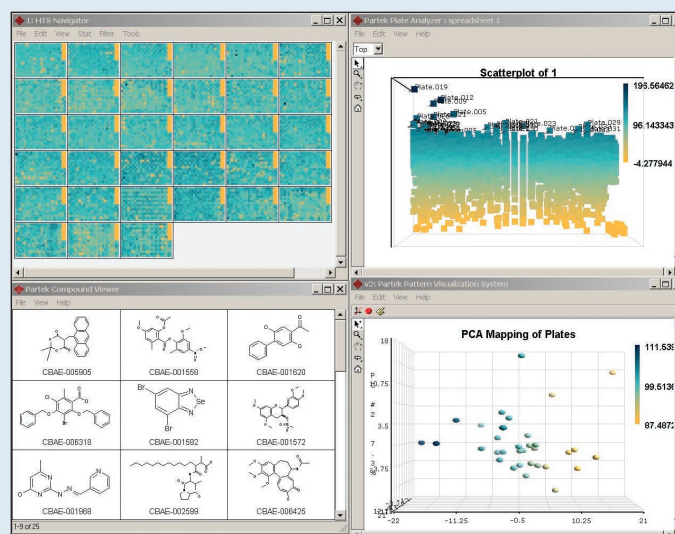
In the quest to find better quality leads faster, discovery biologists will soon have a new tool at their fingertips that saves time validating assay results, identifying outliers, and selecting hits.

MDL is in the final stages of negotiating an agreement with Partek[®], the leading provider of pattern recognition software in science and engineering, to offer a new statistical visualization tool for analyzing plate-based data in MDL[®] Assay Explorer. The integrated module, MDL[®] Assay Explorer Visualizer, allows drug researchers to easily visualize plate-based data in predefined views, interact with the views, and run statistics to validate experiments.

The Assay Explorer Visualizer supports the biological workflow by allowing scientists to focus on research without the distraction of managing disparate technology applications. The module is seamlessly integrated within the comprehensive Assay Explorer biological data management environment. From the Assay Explorer interface a new menu item exposes the visualization power within of a specially designed, run-time version of Partek Pro[™], in an easy-to-use set of views.

Researchers can organize screening plates by similarity, view plates three dimensionally to evaluate trends, and detect outliers or select hits. Utilizing the powerful statistics in Partek, researchers can quickly identify edge effects and trends in large datasets and validate data.

The collaboration with Partek reflects the ongoing MDL commitment to provide integrated tools for biological researchers in the drug



The integrated MDL Assay Explorer Visualizer module allows researchers to easily visualize plate-based data in predefined views, interact with the views, and run statistics to validate experiments.

discovery arena and help biopharma companies improve workflow productivity. For more information visit www.mdl.com or contact your Account Manager. ■

FRAMEWORK

MDL[®] ISIS server products—High value enhancements accelerate customer upgrades

Discovery informatics organizations are continually searching for ways to optimize chemical data management and application development. MDL[®] ISIS customers can accomplish this by upgrading to the latest release of MDL server products: MDL[®] ISIS/Host 5.0, MDL[®] Direct 5.0, and MDL[®] Central Library 5.0. A recently completed customer survey shows that many customer organizations are implementing these new software releases—and that developers and researchers alike are realizing substantial benefits.

According to Dr. Keith Taylor, senior product manager with MDL Discovery Framework, the version 5.0 server release contains many

“must-have” features that were directly requested by customers. For research IT developers, MDL has removed the arbitrary limits on database size and tested a 20-million-structure database—and is planning to build and test even larger databases. [Ed. See this issue’s related article on MDL Direct at AstraZeneca.] The new version also streamlines database maintenance by removing the need to take databases offline for index updates and now supports both Oracle9[™] technology and database replication at multiple sites, which is especially beneficial to global organizations. For chemists and database curators, MDL’s new, enhanced stereochemical representation meets a long-standing industry

need for improved representation of absolute and relative stereogenic centers.

“The survey of MDL ISIS customers indicates that approximately a third of all respondents have upgraded, or are in process of upgrading, to the latest release,” said Dr. Taylor. “We’re supplying capabilities that our customers really need, and the survey reveals that the latest product enhancements—especially the large database capability—are really driving rapid acceptance and deployment of the new system.”

For more information on the most recent enhancements to MDL ISIS server products, contact your MDL Account Manager or submit a request for information at www.mdl.com. ■

Mark your calendars!

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

ADMET1 CONFERENCE

San Diego, California, February 11-13

R&D LEADERS' FORUM

Coral Gables, Florida, March 1-3

MDL UK USERS' GROUP MEETING

London, England, March 4-5

MDL EUROPEAN USERS' GROUP MEETING

Seville, Spain, March 8-10

MDL EUROPEAN BIOLOGY DATA MANAGEMENT EXCHANGE

Seville, Spain, March 11-12

SOCIETY OF TOXICOLOGY ANNUAL MEETING (ToxExpo™)

Baltimore, Maryland, March 21-25
Booth 241

SPRING ACS NATIONAL MEETING

Anaheim, California, March 28-April 1
Booth 210

MDL US USER CONFERENCE

Boston, Massachusetts, May 2-6

MDL US BIOLOGY DATA MANAGEMENT EXCHANGE

Boston, Massachusetts, May 6-7

For more details, go to www.mdl.com. Click on **Company Info** and **Events**.

Developer and Administrator Classes

MDL® Draw Enterprise Edition

MDL® Cheshire

Hview Design, Development, and Optimization

Application Development with MDL® Core Interface

Application Development with MDL® Direct

Application Development with MDL® ISIS

Application Development with MDL® ISIS Object Library

MDL® ISIS/Host Administration

For scheduling and registration information, contact Hannah Kauffman at 800-401-4321, ext. 2107 (h.kauffman@mdl.com) in the U.S. and François Culot at +33-1-45-36-80-23 (f.culot@mdl.com) in Europe.

MDL Web Workshop Schedule

MDL offers 2-hour, interactive Web Workshops for small groups of up to eight participants. These short, focused sessions will quickly bring you up to speed with the MDL products listed below.

For general information on the Web Workshops including topic descriptions, or to register for a scheduled event, contact Veronica Zuniga at edservices@mdl.com or 800-955-0051, ext. 1326.

To schedule special sessions of any of the workshops below (which can also be offered on alternate dates or limited to participants at your site alone), or to arrange custom workshops on topics of your own choosing, contact your MDL account manager or Peg Renery at p.renery@mdl.com or 800-955-0051, ext. 1377.

For more information on MDL training programs, click on **Education** at www.mdl.com.



| Date | AM SESSION (09:00-11:00 Eastern Time) | PM SESSION (13:00-15:00 Eastern Time) |
|---------|---|--|
| Feb. 10 | Exploring DiscoveryGate SM | Exploring DiscoveryGate SM |
| Mar. 9 | Using MDL® CrossFire Commander | Exploring MDL® Metabolite and MDL® Toxicity Databases |
| Apr. 13 | Drawing structure queries with MDL® Draw | Exploring Integrated Major Reference Works TM |
| May. 11 | MDL® ISIS for Excel for the current ISIS user | Creating reports with MDL® Report Manager |
| Jun. 8 | Exploring DiscoveryGate SM | Exploring DiscoveryGate SM |

Putting information into action



Register today for MDL's US User Conference

The 2004 MDL US User Conference is slated for Sunday, May 2 through Thursday, May 6 at the Westin Copley Place in Boston. The User Conference is a great opportunity to discuss the productive use of information in the discovery process with industry colleagues and MDL staff.

Organized around the theme "Information in Action," the conference agenda will include informative keynote and plenary sessions, workshops, product demonstrations, "how to" clinics, the Small Company Forum, a repeat of last year's very popular Vendor Showcase, and a conference dinner at the John F. Kennedy Museum and Library.

2004 Biology Data Management Exchange

You're also invited to stay on with us at Westin Copley Place through Thursday and Friday, May 6-7 for technical workshops, customer presentations, and demonstrations focusing on MDL biology workflow solutions. Learn how your colleagues are using MDL® Assay Explorer, the new MDL® Plate Manager, and other applications to integrate the discovery workflow from chemistry to biology to decision making.



Online registration and hotel registration are available at www.mdl.com/uregister. For conference fee and registration questions, contact Anne-Marie Durkee at Maritz Travel, 925-287-5381, or mdl@maritz.com. You may also contact Anne DeLaFiganiere at MDL at 510-357-2222 ext 1421 or a.delafiganiere@mdl.com.



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