

Using DISCOVERYGate® in medicinal chemistry and cancer research

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esearchers can eliminate undesirable leads early in the lead generation process by quickly accessing information on pharmacological effects, side effects and drug-drug interactions for compounds or compound classes of interest, as well as their corresponding metabolites.

The DiscoveryGate online platform supports this timely drug assessment by providing researchers with quick access to a wealth of information, all from within the same system, from data sources which are otherwise dispersed.

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Case Study

Let us assume that we are interested in checking information known about the reference compound gefitinib, specifically the existence of clinical and pre-clinical data, synthetic protocols and commercial vendors.



Gefitinib (Iressa[®]) is a known EGFR inhibitor recently approved for lung cancer therapy.

Let us further assume that we also work on Epidermal Growth Factor Receptor (EGFR) inhibitors and want to check their adverse clinical effects. Like Iressa, our compound of interest contains a solubilizing morpholine and we want information on its mechanism of action. We need to either buy or synthesize Iressa to use it as a reference standard in our preclinical tumor models.

1. Search the PharmaPendium[™] database for adverse effects and drug safety information (Figure 1). PharmaPendium provides a wealth of clinical and pre-clinical information on Iressa including:

• FDA Approval Package:

- Medical/clinical review with description of clinical trials, key efficacy findings, metabolite profile in humans (with structures), full PK parameters, toxicity findings (>200 pages)
- Pharmacological review (preclinical activity, PK and toxicity in different species (>120 pages)
- Chemistry
- Label
- Mosby's Drug Consult[™] (Drug Monographs)
- Information spanning clinical pharmacology data, pharmacokinetic data, mechanism of action, distribution/metabolism/excretion, drug-drug interactions, etc.
- Meyler's Side Effects of Drugs



 Figure 1: Adverse effects of Iressa from the Label in the FDA Approval Package (search parameter highlighted in results)
 (continued on page 13)

The CNIO has adopted DiscoveryGate because it offers chemists and biologists access to a wide range of information at the interface between the

two disciplines.

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Centro Nacional de Investigaciones Oncologicas (CNIO)

Located in Madrid, the Centro Nacional de Investigaciones Oncologicas (CNIO) was founded in 1998 as Spain's National Cancer Research Center. With approximately 400 scientists engaged in basic and applied research, such as molecular diagnostics and drug discovery, the mission of the CNIO is to:

- Carry out research driving towards the discovery of new and effective diagnostics for cancer patients
- Bring scientific breakthrough to the clinic to ensure advancement is translated into a reality for patients within the National Health System
- Transfer CNIO-developed technology to innovative companies
- Create a new and efficient management system, to break away from the traditional Spanish model

The CNIO is one of the few European Cancer Centers to allocate resources to both basic and applied research in an integrated fashion, thus supporting the interaction of basic research programs with those of molecular diagnostics and drug discovery. Conduct a Drug search for Iressa to display adverse effects/toxicity results (Figures 2 and 3).

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	Abdominal discomfort	no data	no data	3	
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	Abdominal haematoma	no data	no data	1	
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	Abdominal pain lower	no data	no data	1	
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Figure 2: Clicking on the hyperlink under Clinical Data for Abdominal pain displays the clinical data for Iressa

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Figure 3: Adverse effects of Iressa in primary FDA report provided by PharmaPendium.

2. Search for Iressa in xPharm[®], a database of pharmacological information that maps the interactions among agents, principles, targets and disorders for drugs (Figure 4).

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Figure 4: xPharm search results for Iressa showing related records (color coded): two orange codes for Agents (the Iressa concise drug report plus a monograph on tyrosine kinase inhibitors) and one purple color code indicating a Disorder.

(continued from page 13)

DiscoveryGate provides database content that spans the drug discovery spectrum, from target validation to clinical data.



Click on the **Gefitinib** record to review the concise drug report. In xPharm, all references are color coded and records are cross referenced (Figure 5).

When ¹⁴C-labeled getnib was administered orally to albino and pigmented rats, radioactivity was widely and rapidly distributed, with the highest levels being found in <u>liver</u>, <u>kinney</u>, <u>lung</u> and gastrointestinal tract, whereas low levels were found in brain. Levels of radioactivity persisted in melanin-containing tissues (pigmented eye and skin). When administered either orally or i.v., excretion of radioactivity of 1⁴C-labeled getinib by either rat, dog or human occurred predominantly via the bile into feces, with <7% of the dose being eliminated in urine <u>McKillop et al (2004</u>).

Rat									
				Value	Units	Prep. and Route of Admin.	Referen	ce	Comments
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Bioav.	ailability								
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Volum	e of Dis	stributio	n	9-10		l/kg	McKillop et a	l (2004)	
Plasm	a Protei	n Bindir	ig .	87.5 ± 0.5	%	i.v.	McKillop et a	l (2004)	Male (binding independent of dose)
Plasm	a Protei	n Bindir	ig.	8.2 ± 1.4	%	i.v.	McKillop et a	l (2004)	Female (binding independent of dose)
Metal	oolism								
Plasm	a Half-L	ife		2	hrs	i.v.	McKillop et a	l (2004)	
Bio Ha	alf-Life			72	hrs	orally	McKillop et a	l (2004)	65% of the administered radioactivity is recovered.
Cleara	ance			70	%	i.v.	McKillop et a	l (2004)	Within 24 hours.
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DOSE	150	mg/kg		orally				Kuwahara et al (2004)	Mean tumor volume in the gefitinib-treated group was significantly smaller that that in the vehicle-treated group by day 31.
EC50	10-12	umol/l	Malignant rhab	doid	MRT cell	Growth		Kuwahara et al	Gefitinib at 150 mg/kg had a cytostatic effect on established MRT yenggrafts.

Other Information

Web Sites: FDA information on gefitinib: <u>http://www.fda.gov/cder/foi/label/2003/021399lbl.pdf</u> Gefitinib information from MedicineNet: <u>http://www.medicinenet.com/aefitinib/article.htm</u>

Further Reading:

Isobe, Herbst, Onn, Current management of advanced non-small cell lung cancer: targeted therapy, Semin. Oncol., 32(3) (2005) 315-328

Reck, Gatzemeier, Gefitinib ("Iressa"): a new therapy for advanced non-small-cell lung cancer, Respir. Med., 99(3) (2005) 298-307.

Bibliographic References Journal Citations:

Pao, W., Miller, V., Zakowski, M., Doherty, J., Politi, K., Sarkaria, I., Singh, B., Heelan, R., Pusch, V., Fulton, L., Mardis, E., Kupfer, D., Wilson, R., Kris, M., and Varmus, H., EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and entithib. *Tooc. Natl. Acad. Sci. USA. 2024.* (J. 13306-13311)
 McKillop, D., Hutchison, M., Partridge, E.A., Bushby, N., Cooper, C.M., Clarkson-Jones, J.A., Herron, W., and Swaisland, H.C., Metabolic disposition of gefitinib, an epidermal growth factor receptor tyrosine knase inhibitor, in rat, dog and man. *Sanoblocica. 2024.* 34(12), 917-932
 Taguchi, F., Koh, Y., Koizuni, F., Tamura, T., Sajjo, N., and Nishio, K., Anticance effects of 2D6474, a VEGF receptor tyrosine kinase inhibitor, in gefitinib ("Insta"). Sensitive and resistant xenograft models. *2024.* 2012, 1949-922
 Kuwahara, Y., Hosoi, H., Osone, S., Kita, M., Jehara, T., Kuroda, H., and Sugimoto, T., Antitumor activity of gefitinib in malignant rhabdoid tumor cells in vitro and main *acade 2024.* 107 (1989-002)

Citing this Article

Cite this article using http://www.xpharm.com/citation?Article_ID=132036

Figure 5: Pharmacology data (PK and PD) on Iressa in xPharm. Scrolling to the end of the record displays useful links to the primary literature, reviews and related Websites.

Click on the **Tyrosine Kinase Inhibitors** record to review target class and competitor compound information (Figure 6).



Figure 6: Compare Iressa with its closest competitor Tarceva

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3. Search in MDL[®] Drug Data Report (produced by Elsevier MDL and Prous Science) for drug data information on Iressa (Figure 7).

DiscoveryGate[®] MDL[®] Database Browser

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4-(3-CHLORO-4-FLUOROPHENYLAMINC	J)-7-METHOXY-6-[3-(4-MORPHOLINYL)PROPOXY]QUINAZC	OLINE		
Generic Name	GEFITINIB < PROP INN; USAN >			
Formula	C22 H24 CI F N4 03			
Molecular Weight	446.9076			
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**Figure 7:** Pharmacological activity information displayed for the Iressa record in the MDL[®] Drug Data Report database. 'Also found in' links at the top of each DiscoveryGate record offer immediate connections to relevant information on the same compound in other data sources.

Click on the **Metabolite** link to display the Iressa record in the MDL[®] Metabolite Database and return to the FDA Approval Package in the PharmaPendium database (Figure 8).

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**Figure 8:** The results in MDL Metabolite show oxidation of the morpholine moiety in 9 of 13 cases with data on species and enzymes including references. In the PharmaPendium data, five metabolites are identified in human plasma (CYP3A4). O-desmethyl gefitinib has the same exposure and EGFR-TK activity, but only 1/14 of its potency in a cell-based assay. With an elimination half-life of

#### (continued from page 15)

**4.** To find purchasing information for the reference compound, click on the ACD link to retrieve related records in the MDL[®] Available Chemicals Directory database, the world's largest collection of chemical supplier catalogs (Figure 9).

**5.** We can also synthesize Iressa using information provided in multiple data sources containing synthesis information, including the Beilstein Database and ChemInform Reaction Library. Click on **Patent Chemistry** to review synthesis information for patented molecules including retro-synthetic schemes (Figure 10).

The records in the MDL Patent Chemistry Database contain detailed synthetic protocol information for the synthesis of Iressa (Figure 11).

In summary, within a few minutes we reviewed clinical, metabolite, toxicological, patent and adverse side effects data on Iressa. Additionally, we accessed the primary literature and quickly determined whether it is safe and cost-effective to buy or synthesize the reference compound.

The DiscoveryGate platform offers compiled information from various areas of the drug development process and also provides access to the primary literature and reports. The CNIO has adopted DiscoveryGate because it offers both chemists and biologists access to a wide range of information at the interface between the two disciplines. The platform also provides database content that spans the drug discovery spectrum, from target validation to clinical data.

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ACD Registry Number	344258		
Availability	Large and small quantities		
MDL Number	MFCD04307832		
CAS Registry Number	184475-35-2		
Chemical Name and Synonyms :			
<ul> <li>AK0S 91371</li> </ul>			
GEFITINIB     IDESSA			
Molecular Formula	C22 H24 CI F N4 O3		
Molecular Weight	446.908		
Rule of Five	0		
Computed partition coefficent (CLogP)	3.7152		
Molecular weight of largest fragment	446.908		
Number of proton acceptors	7		
Number of proton donors	1		

Figure 9: MDL ACD displays pricing, packaging and supplier contact details for the Iressa compound.





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