

ProteinChip® System, Series 4000

Accelerating biomarker discovery to assays

With over 1000 users world-wide and a large, rapidly growing citation list, Ciphergen's Surface Enhanced Laser Desorption/Ionization (SELDI) technology is the accepted leader in biomarker research. The ProteinChip System, Series 4000 is Ciphergen's newest generation of SELDI instrumentation designed, tested and manufactured incorporating 10 years of first-class biomarker experience.

Designed for today's biomarker research

Ciphergen's new ProteinChip System, Series 4000 incorporates the critical design features demanded by today's clinical researchers and biologists in biomarker research. The Series 4000 delivers improved performance from biomarker discovery to assay offering the fastest route to converting biomarker discoveries to biomarkers assays all



on the same platform. This product note describes the revolutionary new features of this benchtop system, designed to fit into the research plans of any life science laboratory.

Outstanding quantitative biomarker capability

The Series 4000 delivers the best quantitative performance available for biomarker analysis. The system's sensitivity, dynamic range and reproducibility enable discovery and biomarker assays directly on the same platform.

ProteinChip System, Series 4000 Features

Superior quantitation	<ul style="list-style-type: none"> • Raster laser design for maximum spot coverage • Auto laser energy setting • Improved ProteinChip Arrays and protocols • Highest dynamic range
Enhanced sensitivity	<ul style="list-style-type: none"> • New high sensitivity detector • New Ion Source increases ion efficiency • New patented detector blanking reduces noise • Innovative flight tube design
Increased resolving power	<ul style="list-style-type: none"> • Improved fractionation tools increase resolution up to 3000 proteins
High throughput	<ul style="list-style-type: none"> • Unattended runs of up to 168 ProteinChip Arrays
Improved biomarker discovery	<ul style="list-style-type: none"> • Pattern Track™ rapid biomarker discovery to assay • Deep Proteome™-low abundance protein discovery • Biomarker Pathways™-protein interaction pathway discovery & quantitative assays



CIPHERGEN®

The ProteinChip® Company

Sensitivity

The Series 4000 instrument is the most sensitive laser desorption/ionization time-of-flight mass spectrometer available for protein and peptide analysis. It has high-attomole sensitivity for most peptides and many proteins. The Series 4000 is specially configured for sensitivity in the high mass range to allow detection of proteins above 100 kDa. For biomarker discovery and assays, this means you can confidently scan for proteins and peptides in a range from a few hundred Daltons to well over 200 kDa.

Sensitivity – superior detection of proteins above 100 kDa

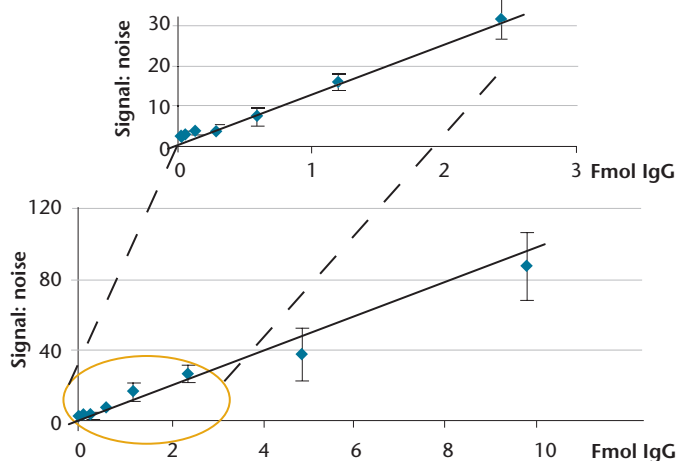


Figure 1: Detection of IgG (150 kDa) using the Series 4000: A quantitation range from 10 fmol to 180 attmol.

Typical reproducibility using the ProteinChip System, Series 4000

	TYPICAL CV%
Internal standard – biomarker assays	< 15%
External standard – biomarker assays	< 20%
Internal standard – interaction assays	< 10%
External standard – interaction assays	< 15%

Sensitivity Features

The ProteinChip System, Series 4000 achieves high sensitivity through the following features:

- A patented conical ion source shape (CISS), efficiently directs desorbed peptides and proteins to the detector to detect the lowest signals possible.
- Synchronized Optical Laser Extraction (SOLE) — a raster scanning laser design ensures complete coverage of the ProteinChip Array spot for total desorption of the sample.
- A superior new detector system includes a patented detector blanking mechanism to reduce noise and eliminate detector saturation from off-scale signals such as the signal from the Energy Absorbing Molecule (matrix signal).
- The revolutionary flight tube design improves sensitivity by minimizing loss of ions as they travel to the detector, while the focusing ion optics maintains excellent resolution for peptide maps for protein identification

Quantitation

The Series 4000 has been engineered to give reproducible results – so you can rely on your data every time! New pre-set calibrations for detector gain, laser energy metering and mass accuracy coupled with automated protocol features ensure high performance results for large scale bio-marker studies. Using the fluid handling robotics system for sample preparation and Ciphergen's ProteinChip Arrays and quality reagents with the Series 4000 offers accuracy and reproducibility every single time!

Dynamic range

Most biological samples present the challenge that the proteins being studied exist in a very wide concentration range. It is reported that for serum analysis, the concentration range of proteins spans at least 10 orders of magnitude; considering albumin (more than 50% of the protein content of serum) down to the lowest abundance proteins observed to date. The concentration for any given biomarker may vary by several orders of magnitude amongst a sample population as well. The Series 4000 has a significantly extended dynamic range analysis capability to meet this challenge.

The system's state-of-the-art electronics maximize the range of protein detection so that the only limitations of dynamic range result from chemical phenomenon. Coupled with CIPHERGEN's high performance ProteinChip Arrays which concentrate proteins of interest several orders of magnitude, the system is capable of quantifying most biomarkers in the attomole range (pg-ng/mL depending on molecular weight). The availability of high resolution pre-fractionation kits and protocols combined with the ProteinChip System, Series 4000 provides the complete solution for analysis of low abundance proteins in serum.

Quantitation Features

The ProteinChip System, Series 4000 achieves reproducible quantitation through the following features:

- *SOLE – raster scanning laser design covers the entire ProteinChip Array spot to produce reproducible results*
- *Automatic settings for detector gain and laser intensity and self-calibrating electronics ensure consistent performance*
- *Automated protocols using robotic fluid handling systems for sample preparation*
- *Reproducible ProteinChip Arrays produced in CIPHERGEN's state-of-the-art automated manufacturing facilities*

Dynamic range of the ProteinChip System, Series 4000

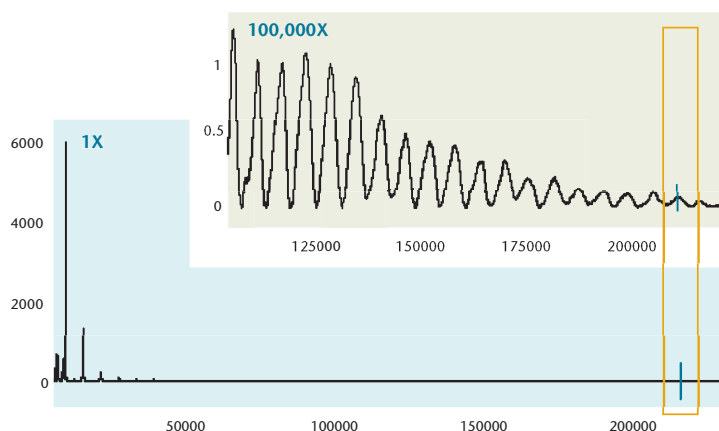


Figure 2: Detection of abundant and low-abundance insulin species. At 1x magnification, the insulin monomer at 5.7 kDa and the insulin multimer (36-mer) at >200 kDa are both on scale. Detection of the multimeric insulin species is shown at a magnification of 100,000x. The intensity ratio of the insulin monomer to the insulin multimer is 1:85,000.

Protein & peptide resolution

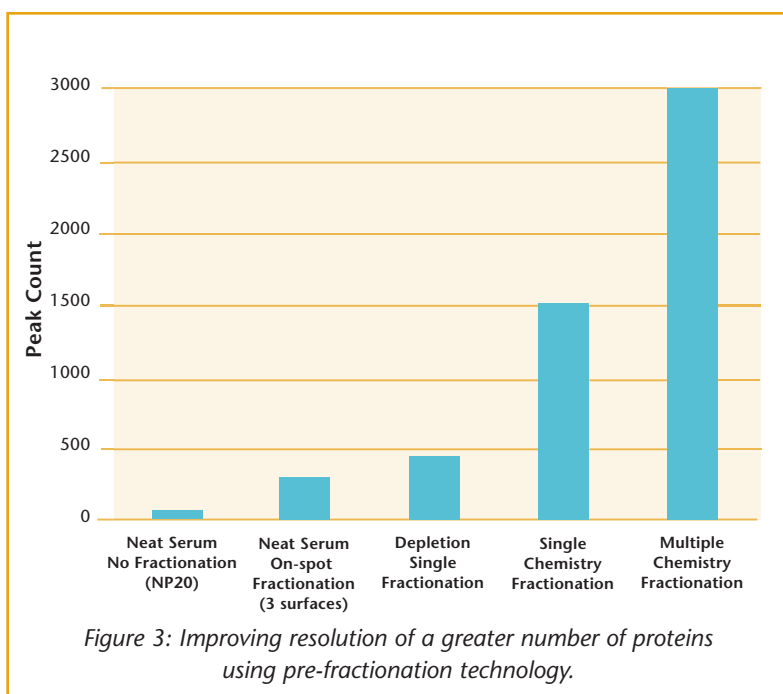
Ciphergen's bead-based reagents, and methods for serum pre-fractionation, together with ProteinChip Arrays, dramatically increase resolution of the number of proteins and peptides that can be detected. Coupled with the improved dynamic range offered by the Series 4000, these methods and reagents add up to the most comprehensive resolution of complex proteome samples.

Spotting neat samples onto arrays typically results in in 50-100 proteins. Applying pre-fractionation tools increases this to 3,000 proteins.

Resolution Features

The ProteinChip System, Series 4000 achieves increased resolution through the following features:

- Multiple ProteinChip Array chemistries selectively retain subsets of proteins from complex samples
- Pre-fractionation technologies to further enrich lower abundance proteins enabling access to the Deep Proteome
- Series 4000 innovative electronics maximize the dynamic range of the instrument to allow detection of a larger number of proteins



ProteinChip System, Series 4000 Software

Included with the ProteinChip System, Series 4000, Ciphergen's powerful software solutions provide the fastest, most effective route for dealing with the large amounts of data generated during biomarker studies. The custom-designed tools include up front sample and data tracking integrated with sophisticated biostatistical analysis packages.

CIPHERGENEXPRESS® DATA MANAGER & BIOMARKERS ANALYSIS MODULE

The Data Manager module includes a robust client-server relational database system for management and tracking of SELDI data. A flexible Biomarker Analysis module provides powerful data mining and analysis capabilities for rapid, automated analysis of multiple experiments over multiple conditions in large project groups for delineation of potential biomarkers.

BIOMARKER PATTERNS™ SOFTWARE

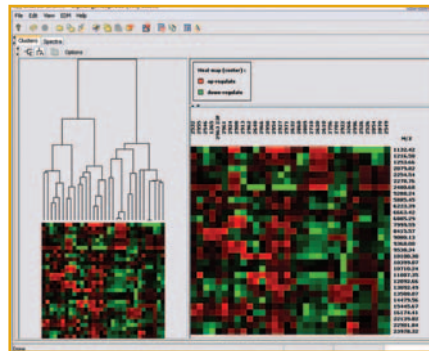
Biomarker Patterns Software (BPS) quickly discovers hidden patterns in SELDI data sets to uncover complex relationships. Using the biostatistical procedure, CART (Classification and Regression Trees) multiple biomarkers are correlated with specific phenotypes to improve sensitivity and specificity over single markers. The output is an easy to interpret decision tree, using a small panel of markers with defined splitting rules. The software translates the discovery of multiple markers into highly predictive biomarker assays.

Principal component analysis: This multivariate analysis tool provides two- and three- dimensional graphic visualization of complex relationships between variables.

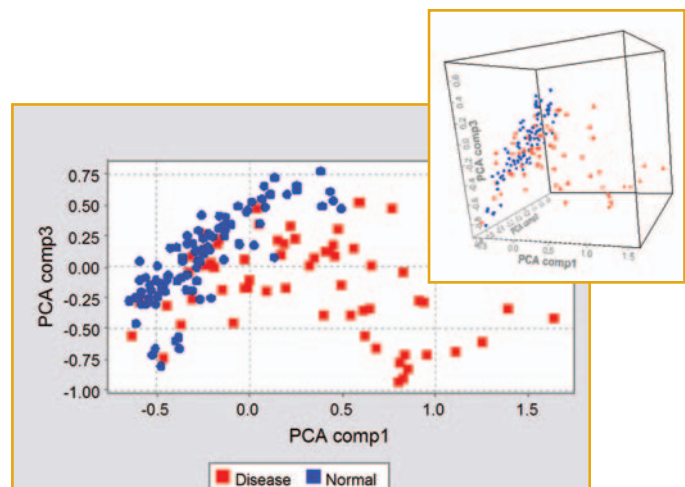
Data Management Features

The ProteinChip System, Series 4000 manages and analyzes data through the following features:

- Bar-coded arrays, and Virtual Notebook feature allow for efficient sample and protocol tracking
- Robust client-server database centralizes data and ensures data integrity
- Intuitive user-interface provides ease of use for both instrument control & data analysis
- Ability to control the instrument from a remote location
- BPS determines multiple biomarker correlation with sample sets in clinical research studies to improve sensitivity and specificity over single marker methods



Hierarchical clustering: The heat map provides a relative-expression view of spectra. Red indicates increased expression and green indicated reduced expression.



ProteinChip System, Series 4000 Personal Edition

ADVANCED PERFORMANCE FOR BIOMARKER RESEARCH AT YOUR LAB BENCH!

The ProteinChip System, Series 4000 – Personal Edition is designed with the biology laboratory in mind. The Personal Edition offers affordable, benchtop, biomarkers research for academic and industrial laboratories. The Personal Edition includes the CISS ion source and SOLE raster scanning laser design for maximum

sensitivity and detection, and the dynamic range capabilities of the Personal Edition are identical to the Enterprise Edition. The Personal Edition can be fully upgraded to an Enterprise Edition at any time.

System configuration

The ProteinChip System, Series 4000 – Personal Edition is designed for complete biomarker discovery, characterization and assay development in low to medium throughput labs. This system includes all of the superior engineered features for sensitivity, dynamic range and quantitation. The complete package includes:

- The Series 4000 Personal Instrument
- CIPHERGEN Express Data Manager – Personal Edition
- Starter Kit package of arrays and reagents
- Biomarker discovery and assay tools
 - Expression Difference Mapping™ kits – for serum fractionation and biomarker profiling
 - IDM Affinity Beads – for interaction discovery mapping studies
 - BioSeptra chromatographic sorbents – for biomarker purification



The ProteinChip System, Series 4000 Personal Edition.

ProteinChip System, Series 4000 Enterprise Edition

HIGH THROUGHPUT: COLLECT THOUSANDS OF SAMPLES AT ONCE!

The Series 4000 – Enterprise Edition is designed for high throughput biomarker analysis research. Thousands of samples can be analyzed, unattended, using ProteinChip Arrays each with a barcode for automated data tracking.

- Automated ProteinChip Array loading – 12 ProteinChip Arrays per cassette, **up to 14 cassettes (168 arrays) at one time!**
- Built-in barcode scanner for ProteinChip Arrays
- CiphergenExpress Software for data tracking, data management and data analysis

System configuration

The ProteinChip System, Series 4000 – Enterprise Edition is a fully automated system for biomarker discovery and assay. The complete package includes:

- Series 4000 Enterprise Instrument
- CiphergenExpress Data Manager
- 14 cassette AutoLoader capacity to automatically feed up to 168 ProteinChip Arrays
- Starter Kit package of arrays and reagents

Additional applications and automated array preparation packages available include:

- Automated Laboratory Workstation with ProteinChip Integration Package
- CiphergenExpress Biomarker Analysis Package – analysis software
- Biomarker Patterns Software – classification and regression tree (CART) analysis software
- Biomarker discovery and assay tools
 - Expression Difference Mapping kits – for serum fractionation and biomarker profiling
 - IDM Affinity Beads – for interaction discovery mapping studies
 - BioSeptra chromatographic sorbents – for biomarker purification

REMOTE ACCESS FOR LABORATORY INFORMATION MANAGEMENT

The Series 4000 – Enterprise Edition has built-in networking capabilities for linking to existing Laboratory Information Management Systems (LIMS), and the instrument can be controlled from a remote site by a designated user.

- Run the instrument from your workstation!
- Networking capabilities
- For extended large-scale biomarker projects



The ProteinChip System, Series 4000 Enterprise Edition.

CORPORATE HEADQUARTERS

Ciphergen Biosystems, Inc.
6611 Dumbarton Circle
Fremont, California 94555
Toll-free: +1 888 864 3770
Tel: +1 510 505 2100
Fax: +1 510 505 2101

UNITED KINGDOM

Ciphergen Biosystems Ltd.
1 Huxley Road
Surrey Research Park
Guildford, Surrey, GU2 7RE
United Kingdom
Tel: +44 (0) 845 230 1151
Fax: +44 (0) 870 350 1152

FRANCE

BioSeptra S.A.
Process Division of Ciphergen
48 Avenue des Genottes
95800 Cergy-Saint-Christophe
France
Tel: +33 (0) 1 34 20 78 00
Fax: +33 (0) 1 34 20 78 78

SCANDINAVIA

Ciphergen Biosystems A/S
Symbion, Suite 253
Fruebjergvej 3
DK-2100 Copenhagen Ø
Denmark
Tel: +45 3917 9741
Fax: +45 3917 9742

SWITZERLAND,

AUSTRIA, ITALY
Ciphergen Biosystems AG
Technoparkstrasse 1
Darwin 2011
CH-8005 Zurich
Switzerland
Tel: +41 (0)1 445 1845
Fax: +41 (0)1 445 1849

GERMANY

Ciphergen Biosystems GmbH
Hannah-Vogt-Str. 1
D-37085 Göttingen
Germany
Tel: +49 (0) 551 30663 0
Fax: +49 (0) 551 30663 20

JAPAN

Ciphergen Biosystems KK
Yokohama Business Park
East Tower 14F,
134 Godo-cho, Hodogaya-ku,
Yokohama, Kanagawa,
240-0005
Japan
Tel: +81 (45) 338 1590
Fax: +81 (45) 338 1591

CHINA

Ciphergen Biosystems Co., Ltd.
12 Hong Da North Road, BDA
Beijing 100176
China
Tel: +86 (10) 67 87 68 23
Fax: +86 (10) 67 87 68 24

www.ciphergen.com

info@ciphergen.com

Product ordering information

ProteinChip® System, Series 4000 Personal Edition	Z500-0013/23
ProteinChip System, Series 4000 Enterprise Edition	Z500-0012/22
ProteinChip System, Series 4000 Enterprise Biomarker Edition	Z500-0011/21
ProteinChip System, Series 4000 Enterprise AutoBiomarker Edition	Z500-0010/20

Related information

CIPHERGEN LITERATURE

ProteinChip System, Series 4000
Technical Note

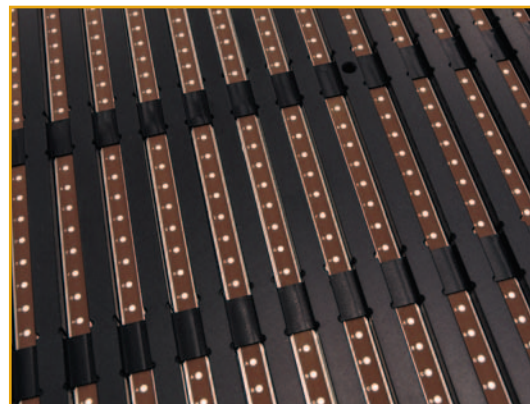


CIPHERGEN WEBSITE

A plethora of related information is available on Ciphergen's website.

For related citations, posters, papers and product literature go to:
www.ciphergen.com/pub/searchPub.asp

For technical documents reserved for users only or to participate in the online discussion group on SELDI technology and its application, go to:
www.ciphergen.com/users



About Ciphergen Biosystems

Ciphergen develops, manufactures and markets ProteinChip® Systems that enable protein discovery, characterization and assay development so researchers can gain a better understanding of biological functions at the protein level.

The ProteinChip Systems are novel, enabling tools that provide a direct approach to understanding the role of proteins in the biology of disease, monitoring of disease progression and the therapeutic effects of drugs.

Pioneering researchers are now taking full advantage of Ciphergen's powerful SELDI-based ProteinChip platform to advance clinical proteomics for predictive medicine.

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