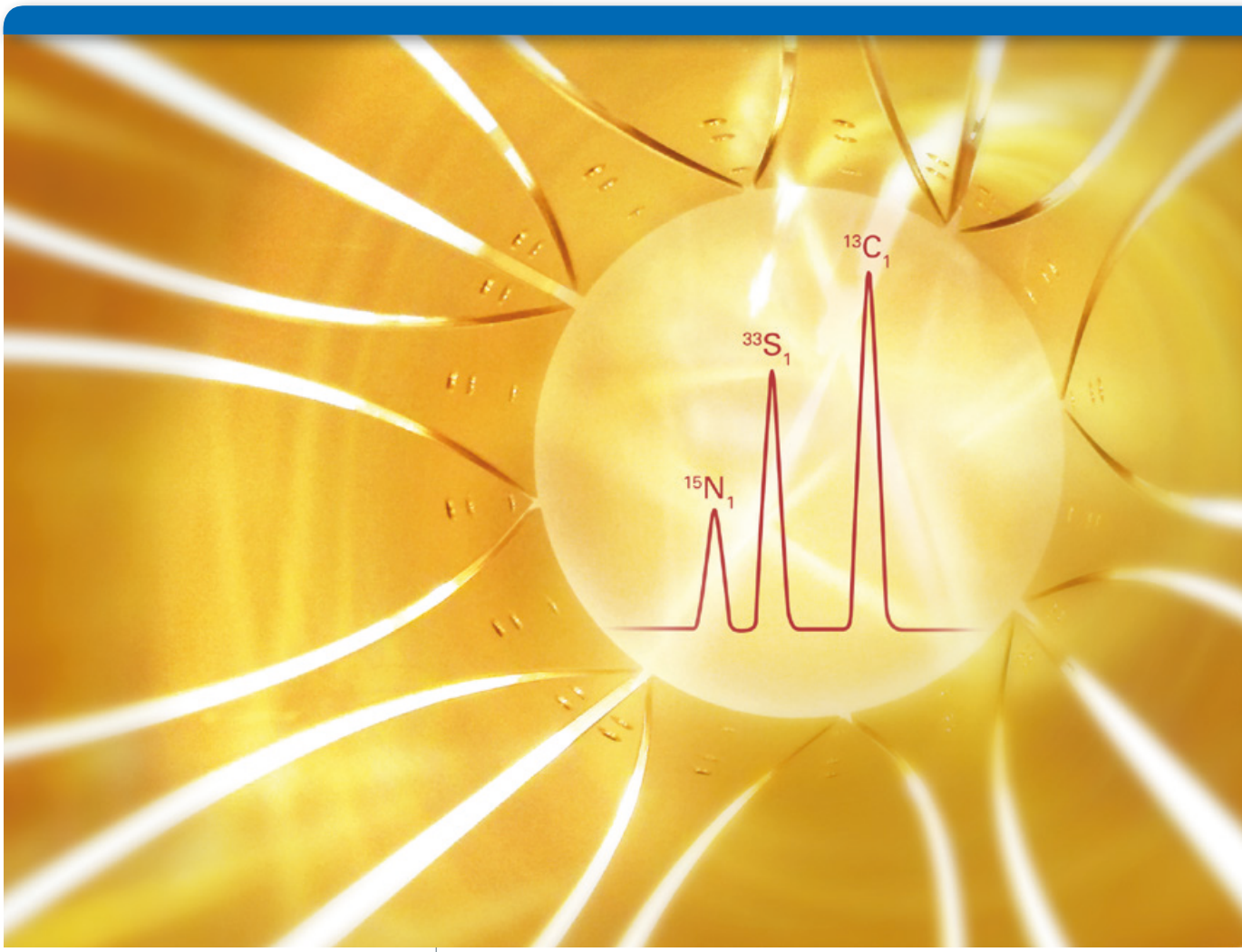


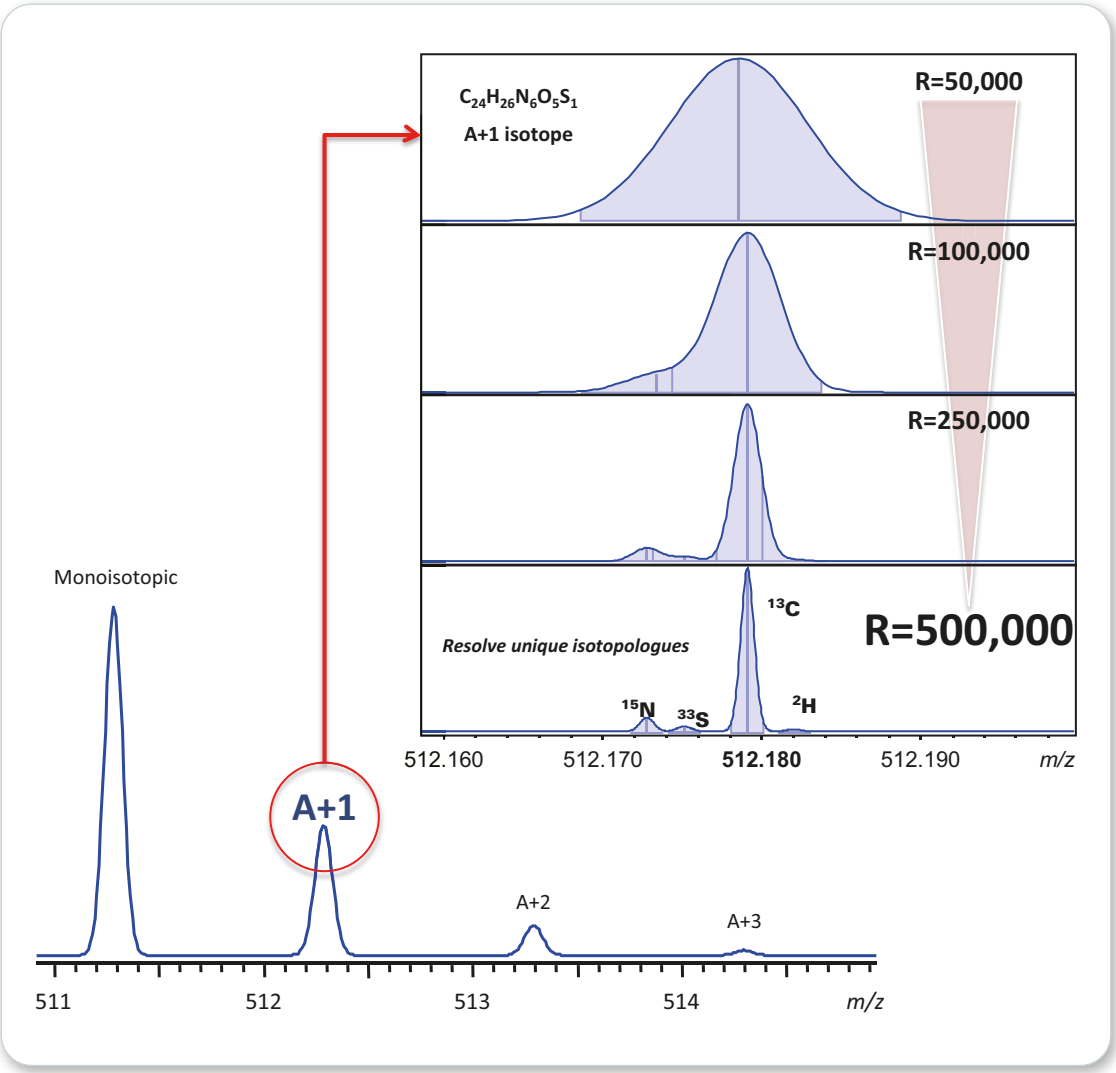
Isotopic Fine Structure

- Beyond the Molecular Realm:
  Unambiguous Elemental Formula Determination

Molecular Identification

Innovation with Integrity

Resolve Beyond the Molecular Realm



View Natures Signatures

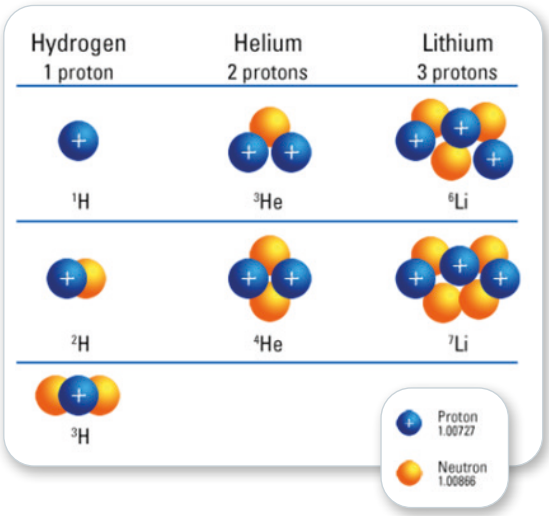
- Discover new chemical information by resolving unique isotopologues
- Confirm fundamental nuclear signatures to reveal the 'true molecular formula', by routinely working at resolving powers (RP) above RP=500,000, having easy access to RP > 1,000,000 when needed
- The exceptional capability of ParaCell™ technology enables you to work beyond the molecular realm*

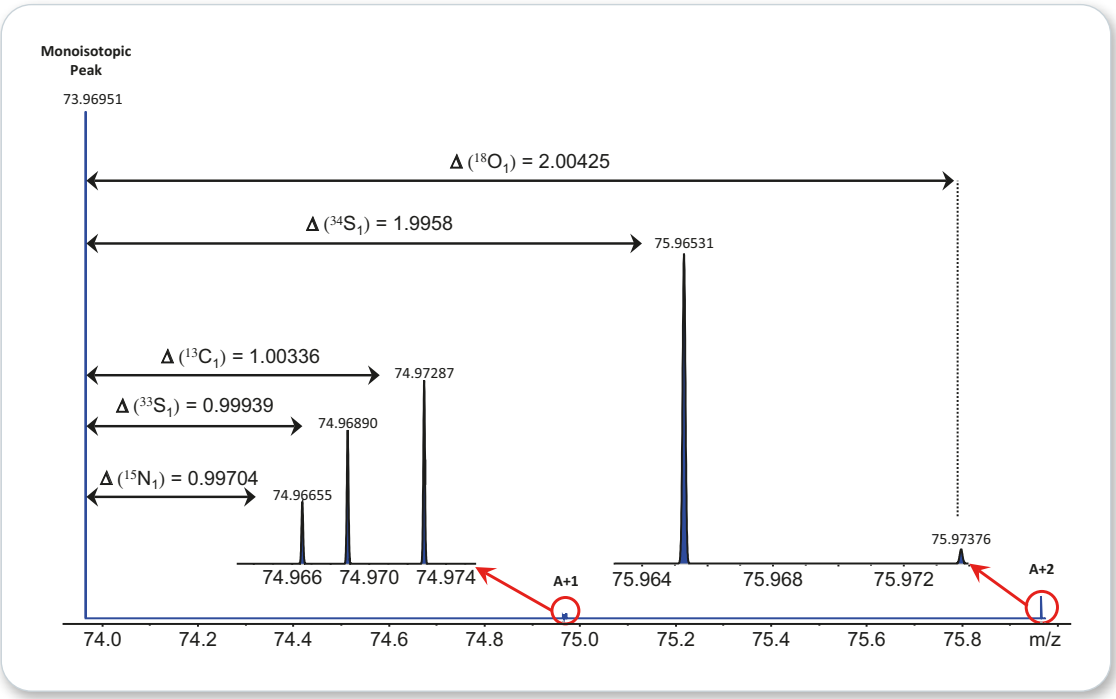
* Boldin, I. A.; Nikolaev, E. N., Rapid Commun. Mass Spectrom., 2011, 25, 122-126.
Marshall, A.G.; Hendrickson, C.L.; Shi, S.D-H., Anal. Chem., 2002, 74, 252A-259A.

Isotopic Fine Structure (IFS)

The value of fundamental nuclear signatures

- Isotopic Fine Structure (IFS) is the unique mass spectral signature arising from naturally occurring isotopes within the molecule being measured
- Classically, the isotopic pattern was described using the isotopes of carbon ($^{13}C_1$, $^{13}C_2$), or more generally A+1, A+2,
(see figure on opposite page)
- The A+1 IFS pattern consists of ^{15}N, ^{33}S, ^{13}C and ^{2}H isotopes, while IFS in the A+2 pattern has ^{18}O and ^{34}S isotopes. Combinations of these elements create unique patterns thanks to different mass defects of the isotopic contributions



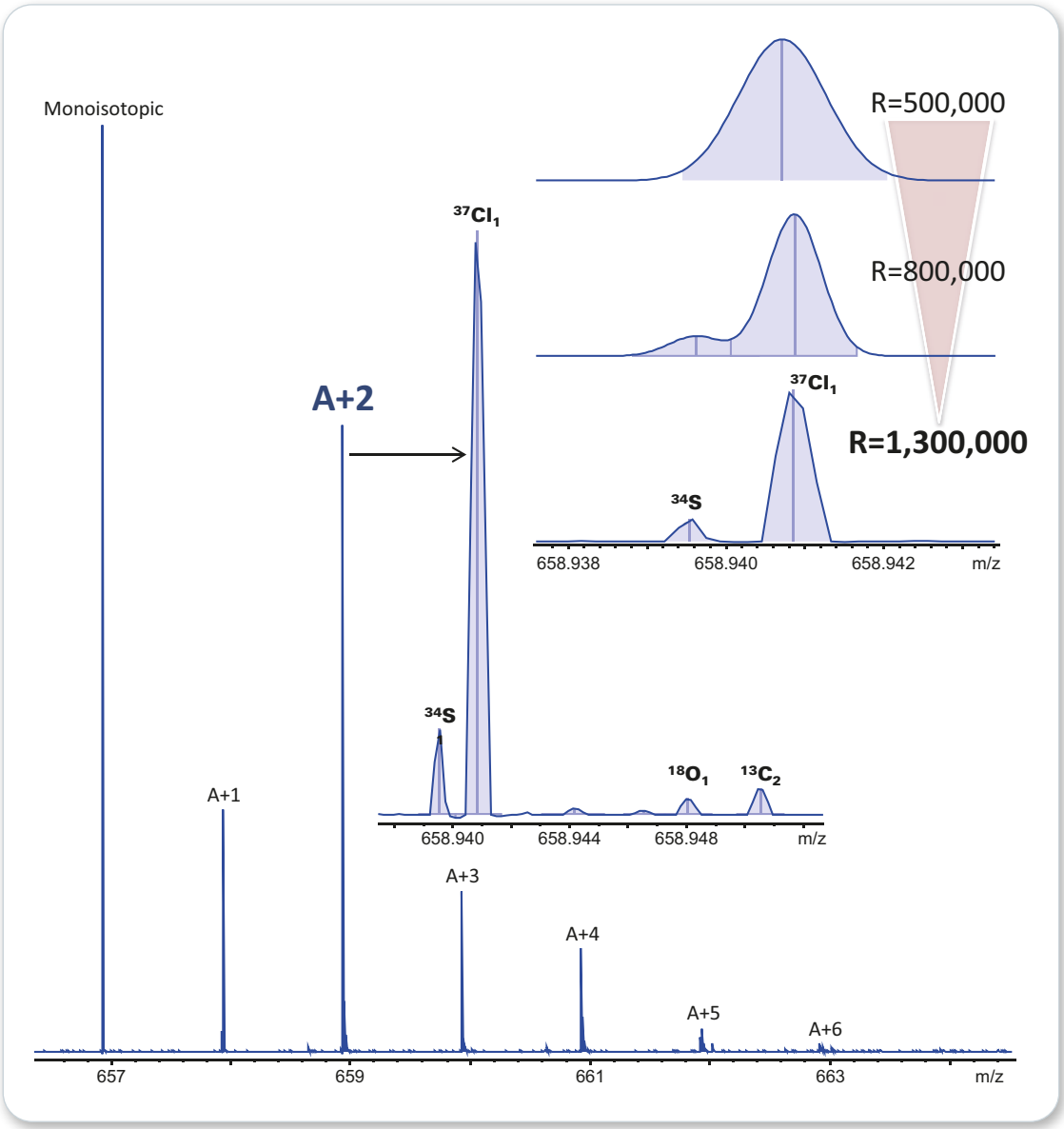


Isotopic fine structure is an EXACT fingerprint for every possible molecular configuration

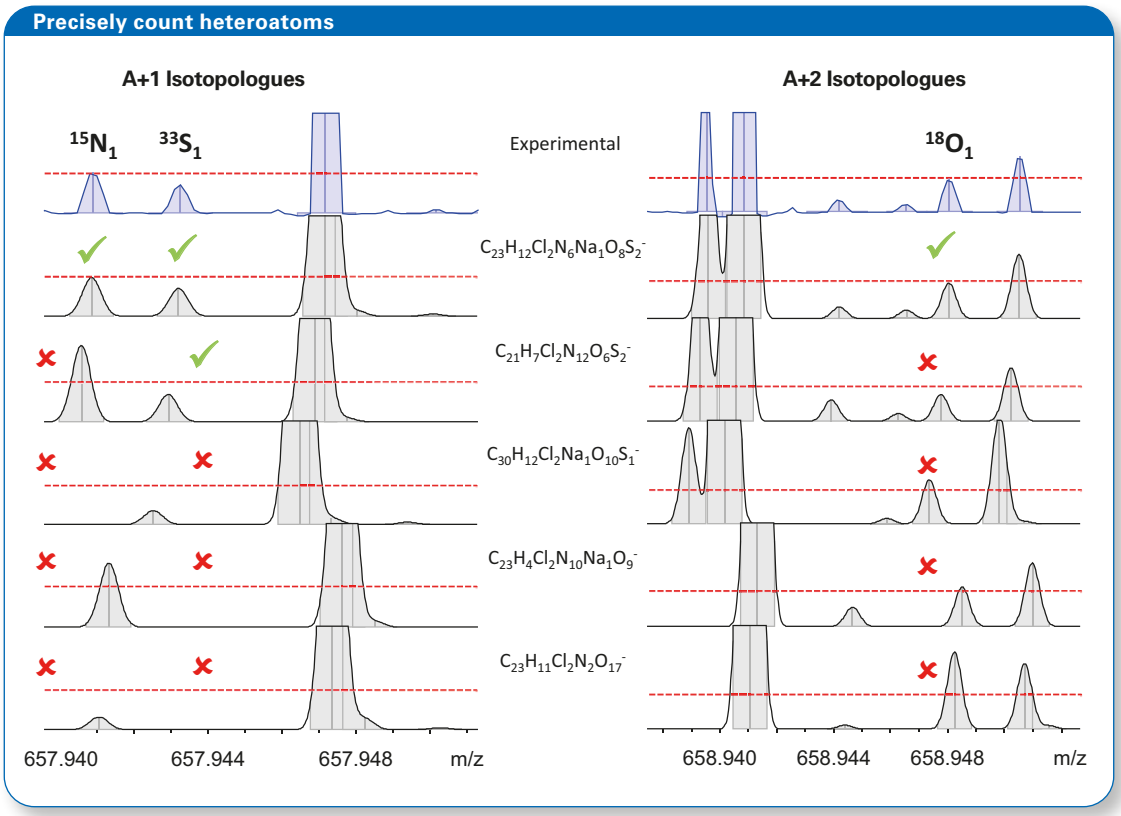
>1 Million Resolving Power

IFS unravels molecular formulae of unknown species

- The strong A+2 isotope suggests Chlorine.
- Sulfur-34 is hidden even at RP = 500,000, so we need the ability to access higher resolution to resolve peaks that are not of equal intensities.
- At eXtreme Resolving powers, isotopologues yield true qualitative molecular information on our unknown



IFS Powered Quantitative Information



Unknown sample is Reactive Blue 4 ($C_{23}H_{14}Cl_2N_6O_8S_2$)

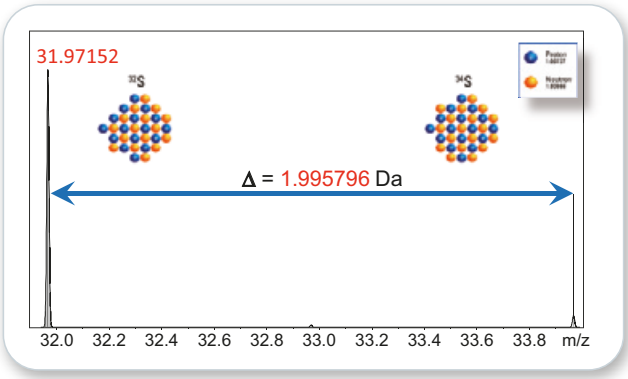
Eliminate Errors Using Heteroatom Mass Spectrometry

- Requires >500,000 RP to do it routinely
- Able to acquire full mass spectrum, not only a subset
- Perfect for quantitation of neutron labelled (^2H, ^{15}N) tags

Sulfur and S-omics

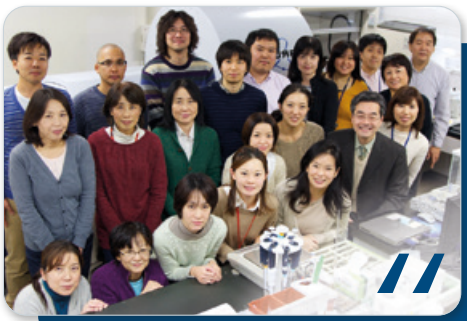
IFS allows discovery of completely new Sulfur containing metabolites with health promoting properties

The IFS approach enables the ability to rapidly identify sulfur containing metabolites and calculate single sum formulas for each, increasing both the speed and accuracy of the workflow. The incredible power of this workflow is that with extreme resolving power and sum formula determination, rapid screening for other heteroatom (N & O) containing metabolites is also possible.



Highlight:

In 2013, Prof. Kazuki Saito, of the RIKEN Plant Science Center (group photo below), was acknowledged with an award for one of the top downloaded papers. Prof. Kazuki Saito has been selected as a highly cited Researcher in 2014 & 2015 by Thomson Reuters in the Plant & Animal Science field and won the 2016 Japanese Society of Plant Physiologists award.



*This S-atom-driven approach afforded an efficient chemical assignment of S-containing metabolites, suggesting its potential application for screening not only S but also other heteroatom-containing metabolites in MS-based metabolomics.**

Breakthrough discoveries by accessing information from fundamental nuclear signatures

References

Ultrahigh resolution metabolomics for S-containing metabolites. Current Opinion in Biotechnology (available online, print 2017)

Chemical Assignment of Structural Isomers of Sulfur-Containing Metabolites in Garlic by Liquid Chromatography–Fourier Transform Ion Cyclotron Resonance– Mass Spectrometry. The Journal of Nutrition (2016)

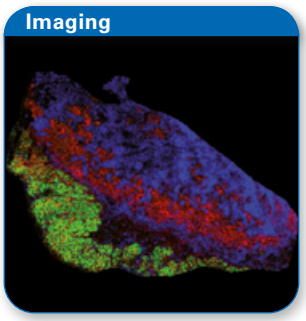
Top-down Targeted Metabolomics Reveals a Sulfur-Containing Metabolite with Inhibitory Activity against Angiotensin-Converting Enzyme in Asparagus officinalis. The Journal of Natural Products (2015)

Revisiting anabasine biosynthesis in tobacco hairy roots expressing plant lysine decarboxylase gene by using ^{15}N-labeled lysine. Plant Biotechnology (2014)

Metabolomics for unknown plant metabolites. Analytical and Bioanalytical Chemistry (2013)

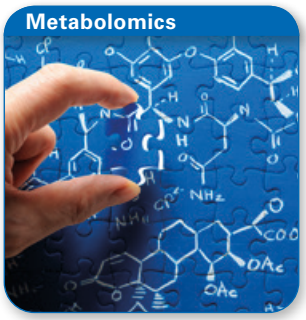
*Combination of Liquid Chromatography–Fourier Transform Ion Cyclotron Resonance-Mass Spectrometry with ^{13}C-Labeling for Chemical Assignment of Sulfur-Containing Metabolites in Onion Bulbs. Analytical Chemistry (2013)

An Invitation to Push the Frontiers of Scientific Discovery



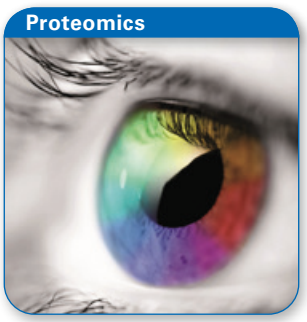
In situ label-free imaging for visualizing the biotransformation of a bioactive pholyphenol
Kim, Fujimura, Hagihara, Sasaki, Yukihira, Nagao, Miura, Yamaguchi, Saito, Tanaka, Wariishi, Yamada and Tachibanad
Scientific Reports, 3, 2805 (2014)

IFS analysis allows for the visualization of spatially-resolved biotransformation based on simultaneous mapping of EGCG and its phase II metabolites. Complements conventional molecular imaging techniques, and can contribute to biological discovery.



Pyruvate carboxylase is critical for non–small-cell lung cancer proliferation
Sellers, Fox, Bousamra, Slone, Higashi, Miller, Wang, Yan, Yuneva, Deshpande, Lane and Fan
The Journal of Clinical Investigation, 125(2):687-698 (2015)

IFS enables the ability to trace biosynthetic pathways. ^{13}C labeled glucose is used to determine fluxomics. High resolution mass spectrometry is used to resolve isotopomers and properly determine the amount of ^{13}C enrichment in various lipids.



Resolving Isotopic Fine Structure to Detect and Quantify Natural Abundance- and Hydrogen/Deuterium Exchange-Derived Isotopomers
Liu, Easterling, and Agar
Analytical Chemistry, 86, 820–825 (2014)

Applies IFS to the HDX workflow. It overcomes a past limitation by using IFS (a real solution). Using ISF, one can simply count the number of deuterons in each one of the peptides, eliminating the need to make any guesses or utilize complex math. A very simple solution to a complex problem.

Synthesis of 7-^{15}N-Oroidin and Evaluation of Utility for Biosynthetic Studies of Pyrrole–Imidazole Alkaloids by Microscale ^{1}H-^{15}N HSQC and FTMS
Wang, Morinaka, Reyes, Wolff, Romo and Molinski
Journal of Natural Products, 73 (3), pp 428–434 (2010)

Isotope labelling is used to follow biosynthetic pathways. IFS allows for an easy calculation of the amount of ^{15}N enrichment as compared to the natural abundance of Oroidin. By feeding live sponges ^{15}N foods, various biosynthetic pathways can be identified.

Isotopic Fine Structure

Breakthrough discoveries by accessing information from fundamental nuclear signatures

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