Introduction to Proteomics
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Lecture – 27
Hybrid Mass Spectrometry Configurations

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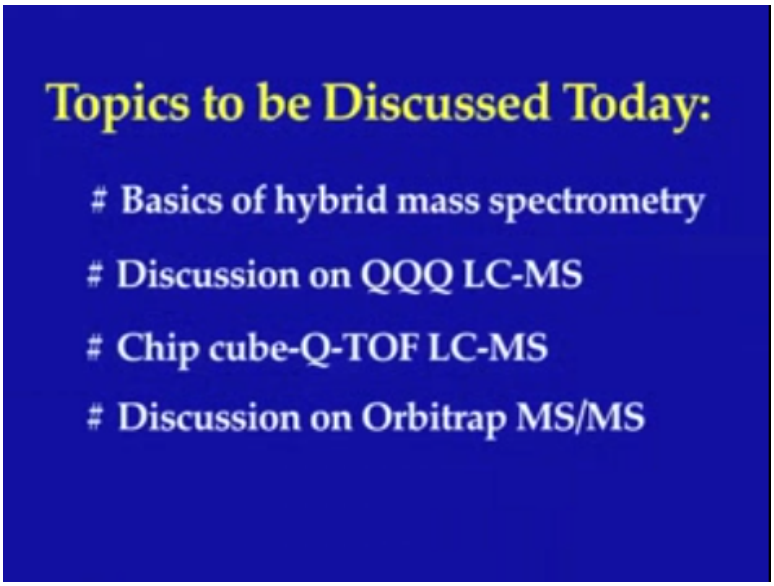

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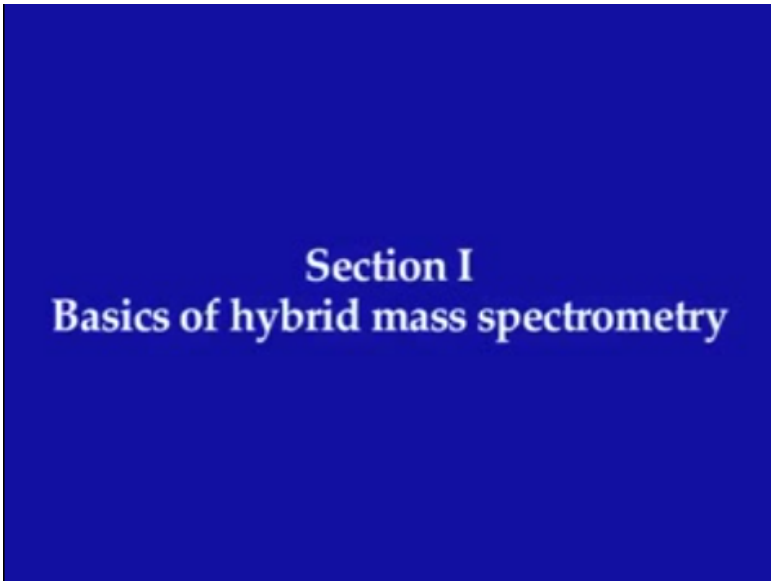

Today, we will talk about hybrid MS/MS configuration. As I have discussed that there are different type of mass spectrometry available and depending upon the mass analysis, how they

can be used to gather different type of MS/MS configuration, hybrid MS/MS have emerged. So, we have discussed that different type of hybrid MS or tandem MS can use for various proteomic applications. There are several new advancements which have happened in this field and to keep up the pace for these recent advancements.

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In today's lecture, I thought to involve a discussion on hybrid MS/MS configurations and talk the two leading companies; one with Agilent Technologies for Q-TOF and triple quadrupole as well as the chip technology and then the Thermo Fisher about the Orbitrap Technology.

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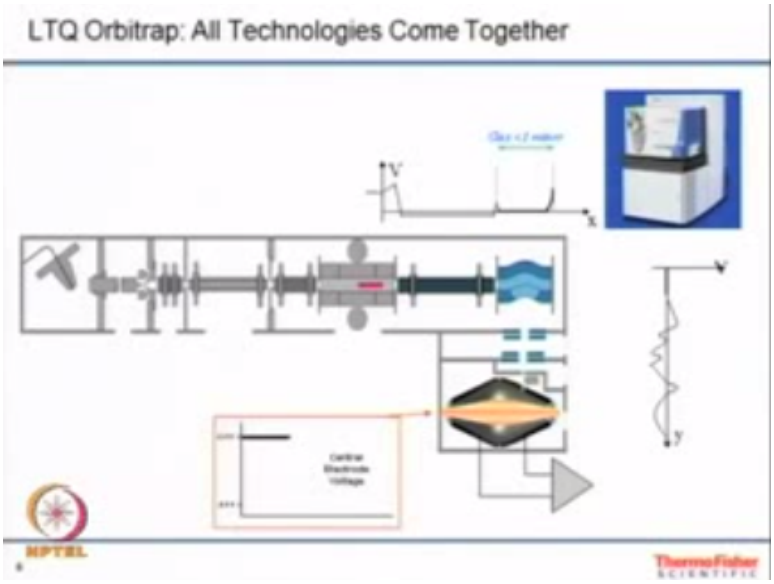

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So, we will discuss about quadrupole time of flight and triple quadrupole. What are the advantages of using these types of hybrid configurations? What is the latest chip technology? How it can be used to overcome several limitations of HPLC based method liquid chromatography which is used prior to the ionization methods.

So, I will discuss these things with one of the leading application expert from Agilent, Mr. Abhijeet and during the short discussion and interview, we will try to provide you an overview of different type of latest configurations available and what are their advantages.

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"Dr. Sanjeeva Srivastava – Mr. Abhijeet Kanungo conversation starts" Hello, it is my

pleasure to introduce Mr. Abhijeet Kanungo who is product specialist in the mass spectrometry division of Agilent Technologies in India. So, welcome Abhijeet for this brief discussion session on mass spectrometry and your experience in this area. So, first of all how long have you been working in the mass spectrometry division of Agilent.

I have spent almost my nine years in mass spectrometry field, our of which I am completing almost four years in Agilent Technologies to take care of Agilent mass spectrometry-based product line to support entire sales team for the technical support. So, can you mention what are the major applications of mass spectrometry on both small molecules and large molecules such as proteomics.

If you ask me, mass spectrometry is a wonderful technique and I majorly classify into two types of applications; one is a small molecule application and second is a large molecule application. Small molecule application involves many-many applications starting from the drug discovery and drug development, forensic applications, food safety analysis, dope analysis, many other applications are available with the small molecule.

But for large bimolecular application, proteomics is one of the application where you really need to explore the possibilities and features what mass spec can support for this application. If you look at starting from (()) (04:19) information, then peptide mass fingerprinting or a post translational modifications or drug discovery or in terms of biomarker discoveries or protein-protein interactions, drug-protein interactions, all such applications are very well possible with mass spectrometry-based solution.

What are some of the major shortcomings you foresee in mass spectrometry-based applications which are currently being used? If you ask me in principle mass spectrometry based proteomics particularly liquid chromatography coupled to electrospray ionisation technique has provide very high throughput application, unbiased identification and characterisation of proteins in biological samples. Moreover, multiple techniques are available today to monitor these changes in protein expression as well as post translational modification studies.

However, people think that mass spectrometry suffers from limited dynamic range or finite acquisition rate, but it is not true. It is not really true. Many new innovations have been implemented to overcome all these issues and all these innovations with the goal to improve detection of low abundance proteins and rare post translational modification studies. So, what MS-based instrumentation and technologies Agilent is able to provide in the field of mass spectrometry.

The field of proteomics is rapidly expanding and it is just about every aspect, any scientist they are looking for each and every aspect which protein research involves from detection and characterisation or to the biomarker discovery and the quantitation studies. Protein analysis has many challenges, so Agilent has a complete solution. If you look at from Agilent offers the chip-based Q-tof integrated proteomics solutions.

An integrated proteomics solution includes advanced LC/MS platforms with unprecedented plug and play flexibility. It is not only instrument, you have to take care of many things starting from the best of mass spectrometry detector, the software which assist you to get the desired information and the sample preparation. So, in actual, Agilent has complete end-to-end solutions for all your proteomics analysis needs. So, what is this best technology which you just mentioned.

If you ask me about the chip-based technique, the very biggest problem comes when you work with the protein sample is you have a very low concentration and low volume of samples and to work with all these low-volume low concentration samples, you have to work the nano HPLC and traditional or conventional nano LCs has a biggest problem of the leakage. As soon as the leak is out, it is very difficult to identify where the leakage will happen.

What is the problem why the leakages cannot be detected? The reason is it has a lot of nuts, ferrules, tubing, fittings, because of that you cannot detect the leakages. In fact, I am carrying a chip with me. If you look at the conventional nano LC, you have a lot of fittings, columns, consumables, because of that any leakages are there, you cannot detect the leakages, right. So, Agilent has come up with excellent solution.

This is the chip technology where you have a sample enrichment capability over here. So, once the sample is enriched by the capillary pump, then the nano flow pump comes and takes sample to the nano columns and in fact you have ionisation source itself on the chip. So, it is completely integrated to avoid all the complications of conventional nano LC. This chip technology has the best solution available today and it is one of the best thing available for any of the proteomics lab.

As you mass spectrometry technology is very much revolutionising all the aspects of life science research and it is heavily used in the clinical proteomics and clinical research, how do you foresee why still the mass spectrometry is not so much used in the clinical (()) (08:47) in the clinical hospitals. In fact, I think the mass spectrometry is waiting to make changes in the industry. It will have a huge impact specially on infectious disease.

If you look at instead of many biological-based methods, one should use the mass spectrometry. Mass spectrometry is very-very simple. It gives you information in minutes and saves, time and money and more accurate results. The mass spectrometry is basically a transformative technique, but the only question is how fast it will be adopted by the scientific community, that is one thing and most of the analyst have perception that this instrument has some limitation but it is not true. This instrument is very simple, easy to use, get results in minutes and more accurate results.

Mr. Abhijeet you rightly mentioned and in fact I will mention here that although the cost is one of the limiting factor for adopting the mass spectrometry-based technologies in the hospitals and clinical setting, but nevertheless even in Mumbai different hospitals when I visited, I saw like lot of these mass spectrometry is actually being integrated for various types of diagnosis. So, that is actually I see one of the very good change in terms of using the technology and directly providing the result for deciding what type of treatment, drug or dose patient should get.

I am 100% agree with you. Even I have seen most of the hospitals nowadays having a mass spectrometry for the clinical applications and majorly, I have see for the small molecule application, but nowadays they are looking for the proteomics-based clinical trial applications. It

starts from various research institutes, most of the research institutes those who are doing research on the clinical-based proteomics, they started using mass spectrometry.

Can you briefly describe about some of these technology which you mentioned as a triple quad and chip-based technologies? Agilent has very good solutions and if you look at the point of triple quadrupole, in fact I have some videos to show you. Look at here, these videos explain you what all techniques are available and how it is useful for proteomics applications. "**Dr. Sanjeeva Srivastava – Mr. Abhijeet Kanungo conversation ends**"

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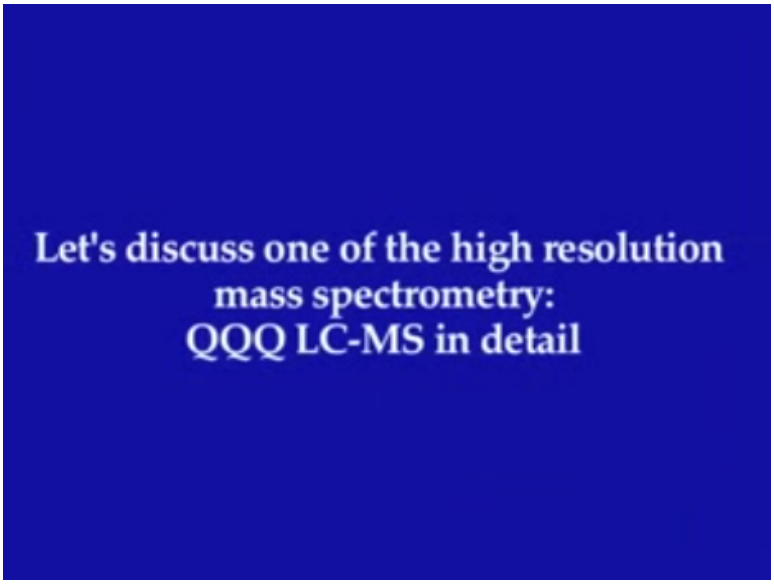

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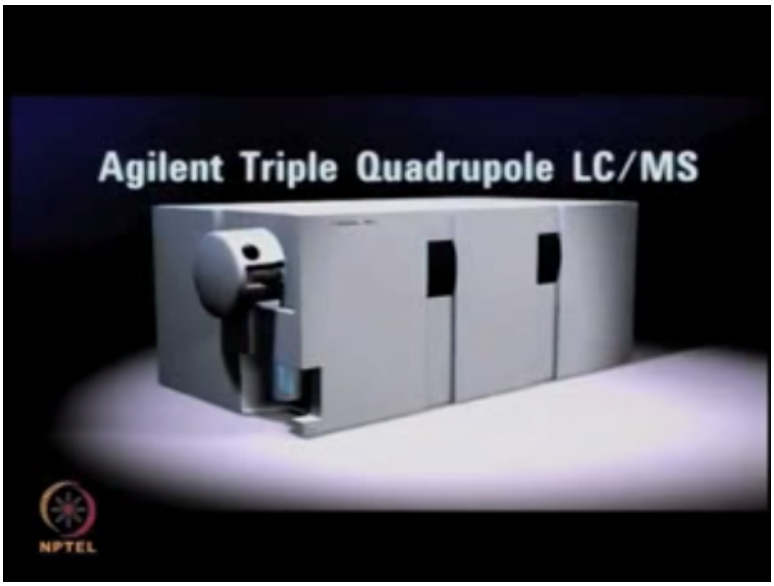

Whether you quantitate drug metabolites, measure herbicide levels in food or determinate contaminant levels in ground water, the triple quadrupole mass spectrometer is unequaled for quantitative trace organic compounds in complex matrices. The Agilent Triple Quadrupole LC/MS delivers outstanding sensitivity, great ease of use and legendary Agilent reliability all at a very attractive price. Great sensitivity starts with superior ionisation technology.

Agilent's LC/MS ion sources use our pattern-hid nebulisation technology and high volume counter flow drying gas. Together, they reduce noise related to incomplete drying of solvent droplets and keep the sampling capillary and ion optics cleaner for reduced maintenance. A thin skimmer aperture carefully matched (()) (12:33) and short capillary to skimmer distance reduce beam broadening.

An octopole ion guide provides better ion transmission over a wider mass, pattern with lenses enhance high mass ion transmission and increase sensitivity over a wider mass range.

The first quadrupole mass filter allows only ions of the target mass to pass through. The hyperbolic shape of the rods enhances ion transmission and spectral resolution. In the hexapole collision cell, precursor ions strike collision gas molecules generating product ions and neutral fragments. Linear axial acceleration and high collision gas pressure simplify operation and

ensure fast, sensitive MS/MS with cross experiment memory affects.

The second quadrupole serves as a mass filter for the product ions produced in the collision cell. For a quantitative analysis of target compound, the second mass filter is operated in a selected ion monitoring mode. In the detector, a conversion dynode operates at 10,000 V to improve sensitivity because the conversion dynode is off the main access of the ion path, neutral molecules miss the dynode, thus eliminating neutral noise.

A secondary dynode helps extend the useful life of the electron multiplier. The electron multiplier has a long life but it is also easily replaced. The Agilent 6410 Triple Quadrupole LC/MS establishes a new standard for value in a triple quadrupole mass spectrometer. It delivers outstanding sensitivity, great ease of use and legendary Agilent reliability all at a very attractive price.

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Now, we have seen how the triple quadrupole is the best technique for the quantitative application. Now, let us look for the Q-TOF technology, how it is useful for the proteomics application.

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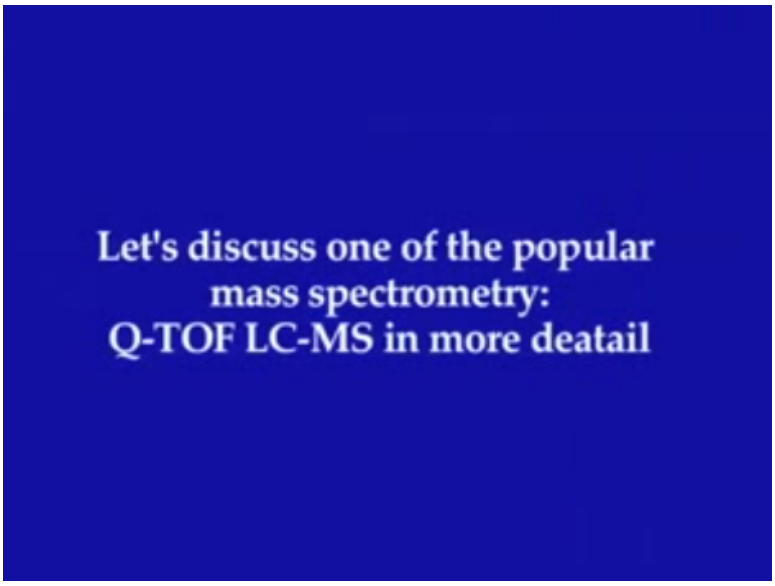

Whether you are identifying proteins and characterising post translational modifications, searching for metabolite biomarkers or finding impurities in pharmaceutical or food, the Agilent 6510 Quadrupole Time of Flight LC/MS is an outstanding choice. It delivers better than 2 PPM mass accuracy for MS and better than 5 PPM mass accuracy for MS/MS. It also delivers wide in-spectrum dynamic range and unsurpassed Q-TOF sensitivity all in a reliable and easy to use system. Great sensitivity starts with superior ionisation technology.

Agilent’s pattern-hid nebulisation technology produces finer droplets and delivers more ions to the mass spectrometer. A second nebulizer introduces reference mass solution that ensures continual mass access correction for the best possible mass accuracy. High volume counter flow drying gas reduces noise related to incomplete drying of solvent droplets and keeps the sampling capillary and ion optics cleaner for reduced maintenance.

A thin skimmer aperture carefully matched hole size and short capillary to skimmer distance reduce beam broadening. An unaccessed optical ion guide provides nearly 100% ion transmission over a wider mass range. Pattern-hid lenses enhance high mass ion transmission and increased sensitivity over a wider mass range. The quadrupole mass filter allows only ions of a target mass to pass through.

The hyperbolic shape of the rods enhances ion transmission and spectral resolution. In the

hexapole collision cell, precursor ion strike collision gas molecules generating product ions and neutral fragments. Linear axial acceleration and high collision gas pressure ensures that all ions exit the collision cell with nearly identical energy. This allows the same mass calibration factors to be applied to MS and MS/MS ions. Result is better than 5 PPM mass accuracy for MS/MS ions.

Another octopole ion guide keeps the ions together while allowing excess collision gas to be pumped away. A quadrupole ion guide flattens the stream of ions for better transmission through the slicer. The slicer reduces variations in the vertical momentum of the ions. Ions with too much vertical momentum do not reach the pulsar. This improves mass accuracy for all ions. The flight tube is constructed of special material with very low coefficients of thermal expansion, so it is less sensitive to temperature changes.

The reflectron compensates from minor velocity differences, improving the resolving power of the 6510. The micro channel plate detector converts the ion signals from electrons to protons and back to electron. This electrically isolates the high voltage flight tube and front of the detector from the signal passed to the electronics. ADC digitizer electronics provide extremely mass accuracy over a broader dynamic range. The 6510 offers outstanding in-spectrum dynamic range for a time of flight instrument.

When you need the ultimate, then LC/MS/MS power and versatility, the Agilent 6510 Q-tof provides it. An ease of use and reliability rarely found in a research grade mass spectrometer. Is it not good the Q-tof technology which we have seen has a tremendous advantage for the proteomics application? We have seen how triple quadrupole and Q-tof works for your application but what about chromatography. I do have some videos which explains you how the conventional chromatography technique and how chip technology has an advantageous feature. Look at the video now.

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It is time to prepare for a new generation LC/MS technology from Agilent HPLC chip /MS. The Agilent 1200 series HPLC chip MS platform takes to a new level of nano-flow LC/MS performance by combing (()) (20:05) with an easy to use plug and play interface that lets you focus on your result. The Agilent HPLC chip/MS platform is based on the Agilent HPLC chip and Agilent HPLC chip/MS interface that is designed for use with all Agilent 6000 series mass spectrometer.

The Agilent HPLC chip integrates enrichment and analytical columns, microvalve connections and memo coated nano electron spray tip on an inert multilayered polyimide film and is smaller

than a credit card. The compact architecture of the Agilent HPLC chip reduces peak dispersion and combines all steps from sample loading through compound ionisation for a seamless operation.

A closer look at the HPLC chip reveals that sample enrichment and separation columns of a nano-flow LC system are integrated with intricate connections and nano electron spray tip for compound ionisation in mass spectrometry. This eliminates 50% of the traditional fittings and connections typically required in a nano-flow LC/MS system which dramatically reduces the possibility of leaks and dead volumes and significantly improves easy to use sensitivity productivity and reliability.

The HPLC chip also incorporates all electrical contacts for the nano electro spray tip and features an embedded radiofrequency ID tag that tracks the usage and operating parameters of the chip. The HPLC chips are housed in the Agilent 1200 series HPLC chip MS interface, the chip cube. The chip cube includes electro sprayed ion source with optics for spray visualisation. HPLC chip loading and ejection mechanism, nano LC connections and micro value switch.

The HPLC chip noting mechanism precisely and optimally positions the electro spray tip orthogonal to the MS inlet for maximum sensitivity and robustness day-in day-out. With the Agilent 1200 Series Nano LC System including Micro Well-Plate Autosampler and loading pump connected directly to the chip cube and HPLC chip is loaded and leak tight fluid connections are established automatically by sandwiching the chip between the rotor and the stator of the built-in multi-board microvalve.

The rotor and stator dock onto the chip and establish a flow path from the nano LC to the ports on the chip surface. Fast movement of the rotor enjoys reliable switching between sample loading and sample analysis positions on the HPLC chip. Replacement of the HPLC chip is simple and can be completed in a few seconds. Let us look at how the Agilent 1200 Series HPLC Chip/MS System can be applied to a typical protein identification analysis.

The Agilent Micro Well-Plate Autosampler loads the digestive proteins. The solvent flow moves

the peptide into the trapping cup. The micro valve changes the flow path. The gradient flow from the nano flow pump takes the enriched sample from the trapping column to the separation column. The peptide are separated just like on a conventional nano flow column. Reduced peak dispersion, yields better separation efficiency and sensitivity.

The integrated nano spray tip enjoys reproducible nebulization of the effluent vital for optimum ionization of compounds and the best results. Proven nano flow LC/MS technology and the new and exciting capabilities of microfluidics combine to form a system that is easy to setup and easy to maintain. Scientists can now get more results faster.

The flexibility of the HPLC chip design and the HPLC chip MS interface microvalve technology in integrating additional chemistries and separation strategies opens up a wide range of potential solutions for many research challenges. Unchipped multiple dimensional nano LC is one of many possible new applications by adding more layer to the HPLC chip additional capabilities such as two-dimensional HPLC, affinity chromatography, and unchip chemistries such as unchip protein digestant are possible.

These new applications and many other such as chips with different column length and packing material are part of Agilent's exiting custom HPLC chip portfolio. Moving beyond protein identification, the new fast flow chip with a sandwich reversed phase titanium dioxide trapping column provides researchers working on post translational modification with a convenient tool targeted at phosphorylated peptides.

Pushing beyond proteomics, the new ultra-high capacity chip with a 500 nano litre trapping column facilitates analyst or pharmaceuticals such as drug metabolism pharmacokinetics with better sensitivity and much lower sample requirement. This will be extremely attractive when the single animal model is implemented in pharmaceutical analysis. The HPLC Chip MS Interface is a standard module within the Agilent 1200 Series LC (()) (25:42) and is fully controllable through the Agilent chem station or Agilent mass under software.

Step by step, chip by chip, Agilent will facilitate new applications in life science, pharmaceutical

and chemical analysis. HPLC Chip MS, a growing trend in LC/MS technology.

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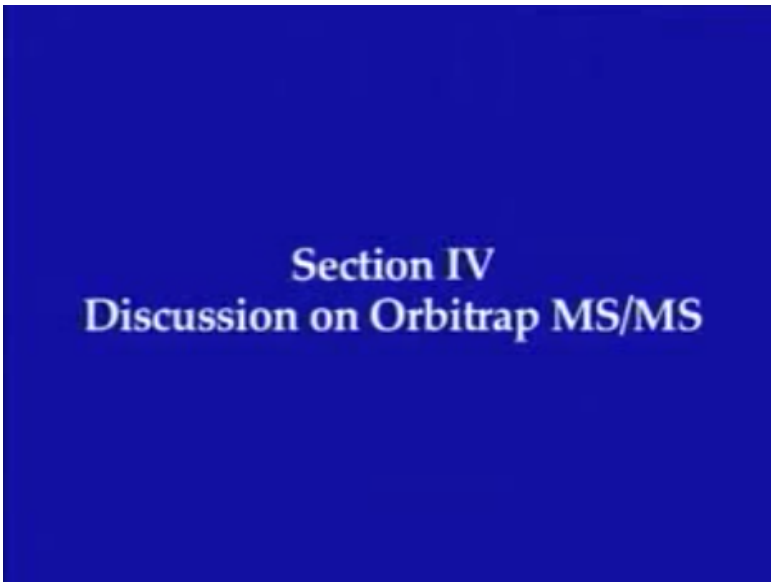

So far discussion on the quadrupole time of flight, the Q-tof as well as triple quadrupole. Now, let us move on to another latest configuration, the Orbitrap which has very much similarity with the ion trap but it is one of the very latest addition to the proteomics workflow where people are applying this for various type of biomarker discovery and different other applications. So, I have invited one of the application expert from Thermo Fisher to discuss about what is the Orbitrap technology, its principle and how it can be applied for different type of applications.

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"Dr. Sanjeeva Srivastava – Mr. Sangram Pattanaik conversation starts" I shall have a

discussion with Mr. Sangram Pattanaik from Thermo Fisher's. It is my pleasure to introduce Mr. Sangram Pattanaik, the product manager LC/MS division of Thermo Fisher. He is working in mass spectrometry area. Hello Sangram. Hello Dr. Srivastava. So, very good to see you in this short conversation about mass spectrometry and some of the latest developments which are happening.

I thought it will be a good idea to talk about some of the latest advancement happening in this mass spectrometry flied and I thought I will invite you and seek your expertise about the Orbitrap and new mass spectrometry applications available. Before I start this conversation, I would like to know little your educational background and maybe about your experience in this mass spectrometry field. Yeah, for the last six years I am looking at the mass spectrometer divisions of different platforms.

In the Thermo Fisher for last one year, I am handling the Orbitrap technology and we ion trap and triple quad systems. Prior to that, I am for last four and five years handling the Q-tof system as well as triple quad from other country vendors. Now, altogether I am there for last 15 years in analytical industry. Okay, so, these are experiences that I carry. Great. So, you have a long interest in this field it seems and you have seen different type of advancement in the field.

So, with that experience can you share what type of major applications of mass spectrometry are currently being used in the proteomics area. Yes, in proteomics mostly there are two basic applications area that people are looking at us with the discovery and the targeted quantification. In the biological discovery, people more talked about proteomics and targeted people are more talking about biomarker validations.

In comprehensive proteomics, people talk would the identify, wants to quantify all in the same sample as well as they look at what is post translational modifications in the whole protein. So, these are the new areas of applications which is going on currently. These are the trends which are going on currently, right. So, I think you rightly mentioned that in fact this is moving more towards quantitation of those proteins, rather than just only identifying them and leaving at only the abundance level which was the case earlier.

So, in that light can you brief us about some of the shortcomings of currently available, mass spectrometry and what challenges we have to overcome to have a really comprehensive coverage of the proteome and to really do various application including the PTM including targeted quantification and different type of application in the biomarker discovery. Yeah, absolutely you have mentioned correctly. The biological markers itself is very complex in nature.

When you have different kind of approach or work flow applications, you look at the analytical solutions which can fulfill that. So, most of the areas of applications, people are more talking about the sensitivity or resolution, mass accuracy. These are the areas. Now, the new area coming up, what kind of different fragmentation patterns or fragmenting care capabilities are record. Those are the areas people are looking at.

So, proteomics is quite competitive and challenging field and right now a lot of emphasis from all the companies in this field for the mass spectrometry, how to provide good solutions for analyzing the complex proteome. So, what type of major mass spectrometry instrumentations are available from Thermo Fisher, currently. As the Thermo Fisher, we have different technology starting from ion trap to Orbitrap but for proteomics platform we normally try to providing them Orbitrap at different work flow solutions.

So, Orbitrap is the main choice of scientist now, if you look at globally as well as in India. If you do not mind, can you just give some overview about the Orbitrap technology currently available. The current Orbitrap we have three different platforms of Orbitrap starting from the low-end to the highest. If you look at the Orbitrap, the Orbitrap is nothing but one kind of ant-trap where the ants moves in a orbit. Just to give you a brief idea it is better to have a small presentation which I can show you.

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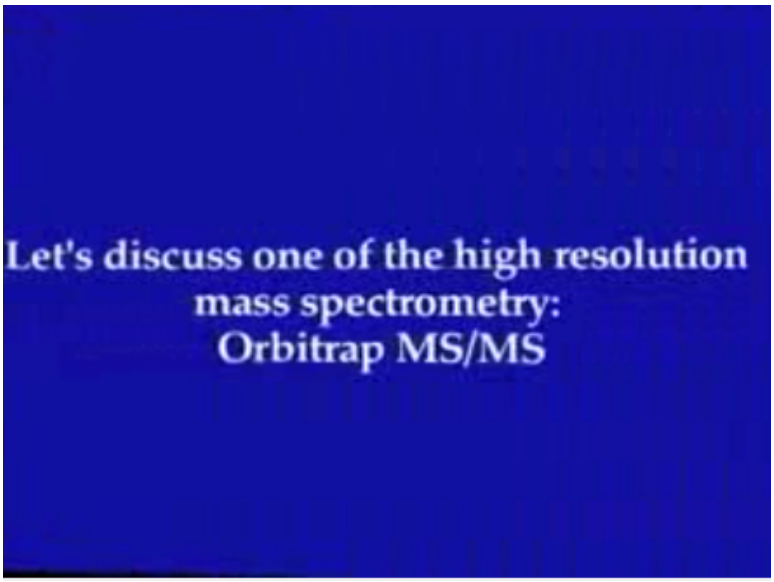

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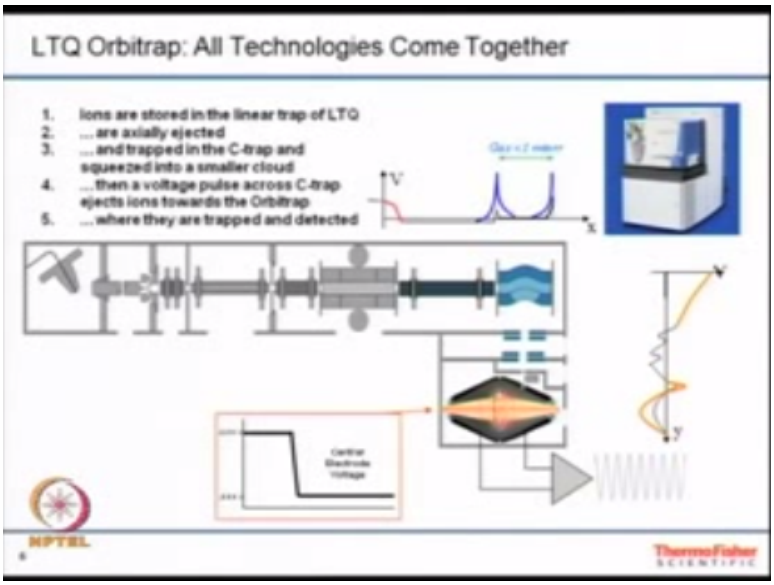

This is how the system looks like. If you look at in the front and (()) (32:02) source and this mass specs are in combinations to each other. We call it is hybrid technology. The first part is a linear ion trap and the Orbitrap. In the first the ionisation, ions are generated from the source that goes to the linear ion trap and it is being trapped there. Once it has been trapped, axially ejected and then goes into the C trap.

The C trap squeezes the ion into the packet and eject that ions into the Orbitrap. Once the ions get injected into the Orbitrap. So probably you are showing those trajectory in the (()) (32:38), right, okay. So, these ions once injected into the Orbitrap it goes into axial most as well as radial

most. We measure the axial frequency of the ion. The frequency which is being measured is transferred into (()) (32:53). If you look at, there is an end electrode which is being connected to the frequency drum which measures the frequency.

Simplest way, you can say it gives you the MS current which has been measured. So, this is how the Orbitrap works. I think you mentioned that you want to show some more detailed path for the path motions. I have a small video which we can also see to that.

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We are just introducing the newest technology that is LTQ Orbitrap Elite. In the LTQ Orbitrap Elite, if you look at this hybrid system which has two this mass spectrometer, the mass spectrometer which is sitting front is a linear trap, that is LTQ Orbitrap LS and then the back end there is the high field Orbitrap or called the Orbitrap Elite.

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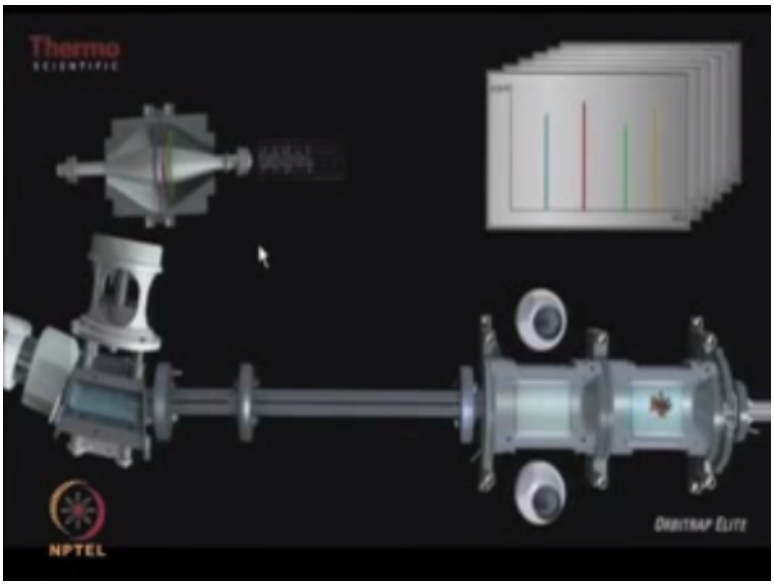

If you look at the schematic of the system, in the front part of the system it is ionisation source which sits on the front. Then, you have the transfer optics and the transfer optics we have a slice which is the newest generation transfer optics. After the transfer optics, we have the transfer tubes and we have the neutral blockers which blocks the neutral which is coming from the source.

Then, we have the octopole and then the ion trap. In the ion trap, we have two resins, one is the high pressure cell and low pressure cell. Then, on the radial, there are two detectors, detector 1 and detector 2 which when you work with the linear trap, the detectors can use for the detections of ion from the linear trap. From the linear trap, it goes to the transfer optics. Then, you have the C trap which dynamically squeezes the ion into packet and allow that ions to go into the high field Orbitrap. Then, you have the (()) (34:42).

Coming back to the ionisation source, the ions generated from the source and goes into the transfer optics and after going from the transfer optics, it goes to be linear trap and the linear trap in full scan modes, the ions are showed into the high pressure cell. Once these ions are showed under high pressure cell in the full scan mode, the ions then change into the C trap through the ion transfer optics. Then, it goes into the C trap.

The C trap does cooling the ion and makes it into the packet of ion, so that the packet of ion

injected into the Orbitrap because the Orbitrap itself is in a static field, so we have injected the ion in tangent to the field. So, once the ions go into the Orbitrap, it moves into the orbit and the frequency is recorded which gives you in turn the mass spectrum.

If you want to work the linear trap and the Orbitrap at the same time, you can draw both at the same time. In the linear trap, the ions get stored and fragmented and then it ends into the Orbitrap. So, you can have the MS as well full scan MS/MS at the same time, but from that in addition to the full scan MS and MS/MS, you can have also low resolution scan from the linear trap. So, this is what you can obtain from the Orbitrap.

So, it was very good to learn about the Orbitrap technology and how it works. So, finally I would like to ask you what is your recommendation for mass spectrometry user, what are different challenges occur in this field and maybe your final message to the users of mass spectrometer. It is very difficult to answer but in a simplest way I can tell you it all depends on the applications area.

If you look at the selection of an instrument depends on what kind of applications people are looking at. It is more of a thing which people should look at more global scenario. How people are going into doing applications in those area. It is also now of a thing, if can have an instrument, you can generate a lot of data but it all depends on interpretations of those datas and it has to be application oriented. So, you mentioned very rightly that mass spectrometry has infinite possibilities.

It has tremendous potential and depending upon your application, one can explore seamless possibilities taking out from the mass spec and how one can interpret those data has actually become more challenging and people are coming up with very creative ways of analyzing the data for different applications. So, with that I will conclude this interview and I will again thank Mr. Sangram for sharing your Orbitrap and different experience of mass spectrometer with us.

Thank you, thank you very much. "**Dr. Sanjeeva Srivastava – Mr. Abhijeet Kanungo conversation ends**".

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Alright, so as you have seen the two interviews and discussion on different type of hybrid MS configurations, we talked about quadrupole time of flight, triple quad and Orbitrap technologies. You have also seen the latest advancement in the field, the introduction of chip-based technology. These are just few examples. There are many other goods configurations available from various manufacturers in the field.

This interviews were mainly intended to showcase different type of hybrid MS configurations available and more latest technologies which are trying to overcome the HPLC-based methods and their limitations. There are many other good manufacturers available and these two are just two examples to showcase different type of advancement. Now, we will continue our discussion on different type of mass spectrometry-based applications in the next lecture, thank you.

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Acknowledgement

- Mr. Sangram Pattanaik ThermoFisher scientific.
- Mr. Abhijeet Kanungo, Agilent Technologies