THERACAT

Teva's contribution

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R & D IL - Teva Pharmaceutical Industries, LTD

European Training Network THERACAT

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TEVA – R&D Building Kfar Sava

Content

- Goals
- Teva Team
- Roles and Capabilities
- Regulatory and Technological Profile of a Nano Sized Suspension
- IMMS
- Research Focus

Goals

- To deliver the pharmaceutical regulatory platform for researchers training and development of new chemical moieties as nanomaterials for biorthogonal catalysis

- To enrich the consortium with practical knowledge on bringing new molecules to the market - formulations, regulations, procedures, scaling up and economical aspects

- To deliver an analytical state-of-the-art platform in order to gain detailed understanding of the behavior of biorthogonal catalysts in the biological environment

Teva Team

THERACAT – Teva Leader		Bianca Avramovitch, PhD
THERACAT – Teva Coordinator Preclinical Specialist		Neta Zach, PhD
Analytical Technologies Specialist		Yousif Ayoub, PhD
Formulation Specialist		Hemda Cohen, PhD
Macro Molecules Specialist		Turi Komlosh, PhD
CMC Development Specialist (chemistry & manufacturing controls)		Tal Hasson, PhD
Chemistry Specialist		Sharon Gazal, PhD
Ad hoc experts support:		Vera Weinstein, PhD

Roles and Capabilities

- **Provide the regulatory platform for the quality, safety and efficacy** of medicines, providing answers to questions raised from development thru commercialization stage

- **Develop drug products (chemistry and formulation)**
  - at the molecular chemistry level (impurities)
  - at the physical structure level (polymorphism)
  - at the powders level characteristics (particle size & shape)
  - at the formulative level for optimal bioavailability (minimum dosage for desired efficacy)
  - at the final drug product level (packaging and stability)

Roles and Capabilities

- **Explore technologies** and **processes feasibility** from diverse fields as medicine, engineering, analytics, physical chemistry and physics:

Hyphenated technologies targeting separation, identification, entities distribution and grades	
Micro Raman	IMMS (UHPLC with Ion Mobility Mass Spectroscopy)
Transmission Raman spectroscopy (TRS)	MALLS, RI, Corona, Viscotek, detectors on LCs (UHPLCs, HPLCs, GPCs)
Microscopy FTIR	CE with PDA and LIF detectors
SEM	Particle size distribution (PSD) based on laser diffraction, imaging: Malvern 3000, Morphology, DLS, QicPick, Microscopy
NMR	GC -HS+FID/MS
Micro Computation Tomography (micro CT)	
Optical coherent topography (OCT)	ICP-MS

Regulatory and Technological Profile of Nano Sized Suspensions

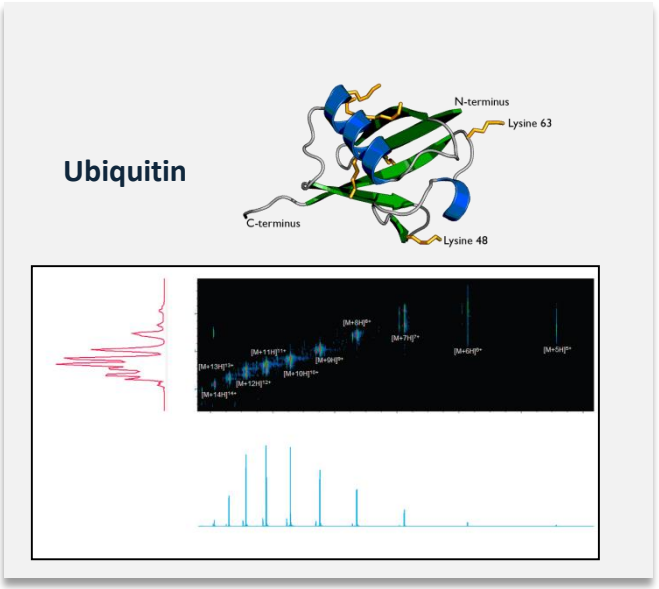
Measurement	Technology	Comments
Appearance		Preferable an instrumental measurement and not a subjective one
Identification in Drug Product	FT-IR Microscopy	Spectroscopic methods required in addition to chromatographic ones
Assay Impurities	LC, GC, CE	Method chosen depends on the sample: Volatility, Chromophors, Detection Limits
	ICP-MS, ICP-OES, AA	Inorganic Elemental Impurities
Impurities (including enantiomers) Stability program for Drug Product	mini-column centrifugation ultracentrifugation dialysis	Membrane permeability evolution must be followed in time Distinction should be made between encapsulation of a molecule in the internal aqueous volume and absorption of the molecule on the membrane
Excipients Characterization	Chromatographic: LC, GC, CE, GPC Solid State: PSD, degree of polymerization,...	Assay, Impurities, Residuals, Similar with any API characterization

Regulatory and Technological Profile of Nano Sized Suspensions

Measurement	Technology	Comments
Particle Size Distribution (PSD)	SLS DLS Microscopy (Raman, SEM, ..)	SLS: for micronized material DLS: from 1nm to1mm (from MW~1000DA)
Polymorphism	X-ray, DSC, FTIR, Raman SS-NMR	1.When microscopy is added on it is lowering the detection limits while keeping the specificity 2. When detectors are added to DSC(TGA), FTIR – the method can become specific.
Surface Area	NMR	Wetted Surface Area - Suitable for concentrated micro- and nano-suspensions Supplier: Acorn AreaTM
Packaging Related	Chromatographic and Physical Properties	Extractables and Leachables Permeability, Consumers Oriented Design

IMMS: Ion Mobility Mass Spectroscopy

- Greater separation of lipids and glycopeptides
- Characterization of structural conformations and isomeric compounds
- Greater numbers of trace level peptides in complex matrices
- Preservation of structural fidelity of metallo-proteins in liquid phase solutions



IMMS: Ion Mobility Mass Spectroscopy

IMMS achieves a very high peak capacity since it can simultaneously combine the resolving power of UHPLC, IM, and mass resolution without compromising sensitivity performance

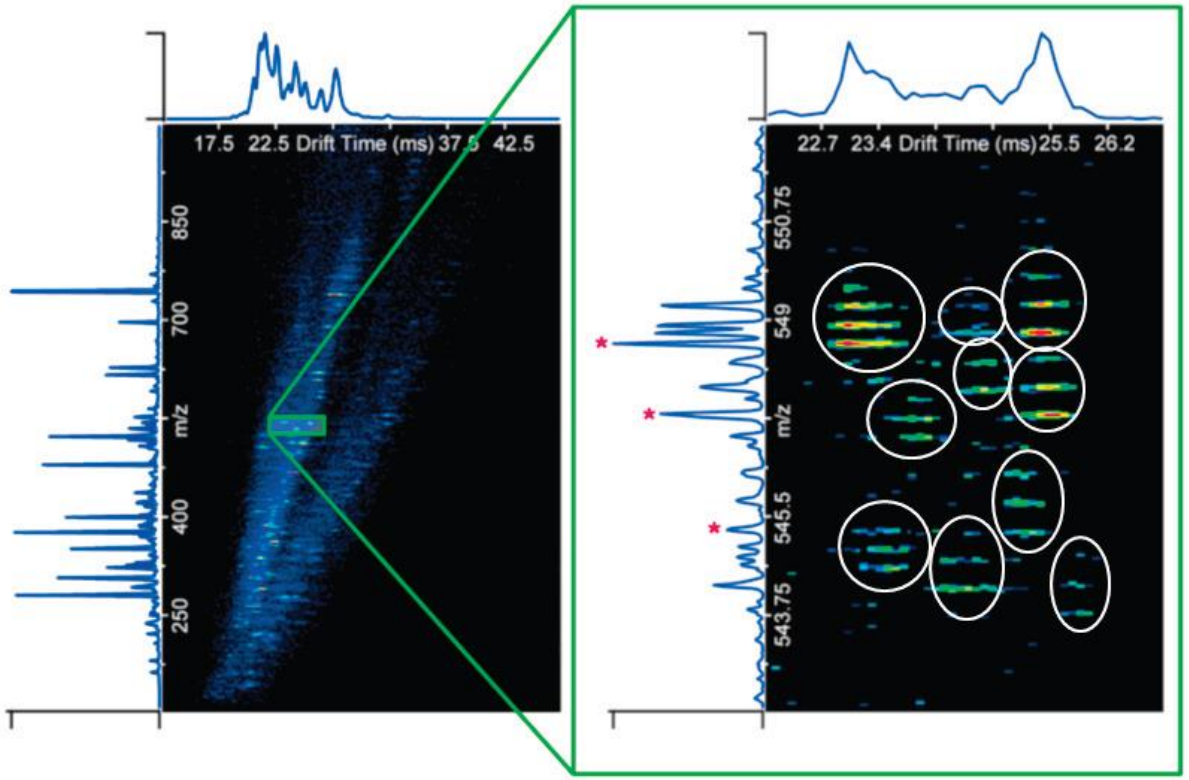
Peak capacity =

UHPLC resolving power × IM resolving power × MS resolving power × fraction orthogonality

Peak capacity: the maximum number of peaks that can fit in any multidimensional method

IMMS: Ion Mobility Mass Spectroscopy

- The m/z versus drift time plot shows the separation of tryptic peptides derived from mouse blood plasma sample spiked with 20 reference peptides.
- The sample was subjected to 15 minutes LC separation before IM-QTOF analysis.
- The inset shows a zoomed in region of the 3D plot where 10 peptides were identified for the LC-IM-QTOF experiment.
- The same sample was run with a 100-minute LC gradient using LTQ-FT-MS instrument that yielded only three identifications, as indicated by asterisks.



IMMS: Ion Mobility Mass Spectroscopy

VANDERBILT UNIVERSITY

John McLean of Vanderbilt University on IMS/MS :

"With IMS/MS you can rapidly analyze something as complex as a cancer biopsy and see which masses correspond to peptides, lipids, or carbohydrates. You can really integrate all of those 'omics' strategies."

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Research Focus of TEVA THERACAT Team

1. **Develop high resolving methods** for characterizing the species developed by TAU – TEVA team and any other interested consortium partners, methods which will be able **to monitor** the researched processes, the synthesis and biological evaluation of the new species.

2. **Develop a comprehensive training program on scientific and regulatory requirements of new targeted drugs.**

   This program will include all steps required for a successful filling, from drug substance/s synthesis and characterization to formulative development, manufacturing scale up, packaging and stability studies.

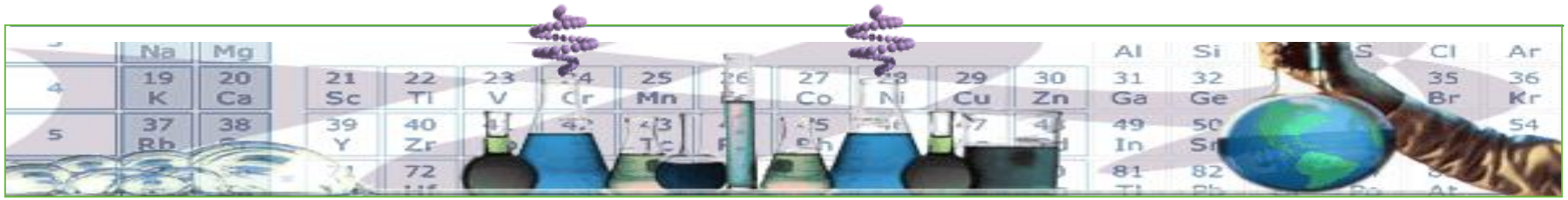
Research Highlights

1. **Design and synthesis of polymer-based drug delivery systems (DDS):**
   Linear and/or micellar polymers (as facilitated by TAU - TEVA THERACAT researchers, as per the team involved)

2. **Carbohydrates – receptors expression mapping by IMMS**
   Models: Melanoma and/or PDAC cells

3. **Carrier/polymer conjugation characterization** by IMMS, Micro Raman, CE-LIF, and additional, as relevant

4. **Comparative profile mapping for cancerous/noncancerous tissues** by applying new hyphenated technologies



THANK YOU!