TEVA Presentation

Meeting 1
Eindhoven, 26th March 2019

Innovative Training Networks (ITN) – Marie Skłodowska-Curie Actions
H2020-MSCA-ITN-2017 (THERACAT-765497)

Contents:

- Institution introduction
- Teva Team
- Update on Teva Team recent research
- Recruitment
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Teva Leading Generic Medicines

1 in 7
Rx in the US

1000+
Launches in 2017

Top 3 position
in 25 markets

550+
therapies

1 in 8
Rx in the UK

1800+
Molecules

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Teva Leading Specialty Brands

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Global R&D Representatives

- Israel (3 sites)
- UK (2 sites)
- Hungary
- Romania
- Ireland
- Croatia
- Iceland
- US (5 sites)
- Mexico
- Chile
- Argentina
- India (2 sites)

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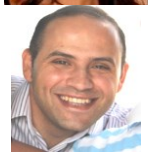
Teva Team

Principal Investigator		Bianca Avramovitch, PhD
Teva Coordinator, **Academic Affairs and Networks**		Tal Yoetz, PhD
Analytical Technologies Specialist		Yousif Ayoub, PhD
Formulation Specialists	 	Aviram Spernath, PhD; Tamar Gordon, PhD
Macro Molecules Specialist		Turi Komlosh, PhD
CMC Development Specialist (chemistry & manufacturing controls)		Tal Hasson, PhD
Chemistry Specialist		Sharon Gazal, PhD

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Update on TEVA Team Research Activities

Vast development knowledge from idea to product on:

- Therapeutic substances
  - small molecules,
  - peptides,
  - proteins
  - complex materials
- Pharmacology and toxicology studies
- Lead compounds selection
- Routes of administration (from tablets to digital inhalers products)
- Complex pharmaceutical formulations development and manufacturing
- Drug substances and products characterization by state of the art analytical technologies
- Regulatory affairs and submissions, launches and products support

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 NMR Micro Computation Tomography (micro CT) Optical coherent topography (OCT)	Particle size distribution (PSD) based on laser diffraction, imaging: Malvern 3000, Morphology, DLS, QicPick, Microscopy GC -HS+FID/MS ICP-MS

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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

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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

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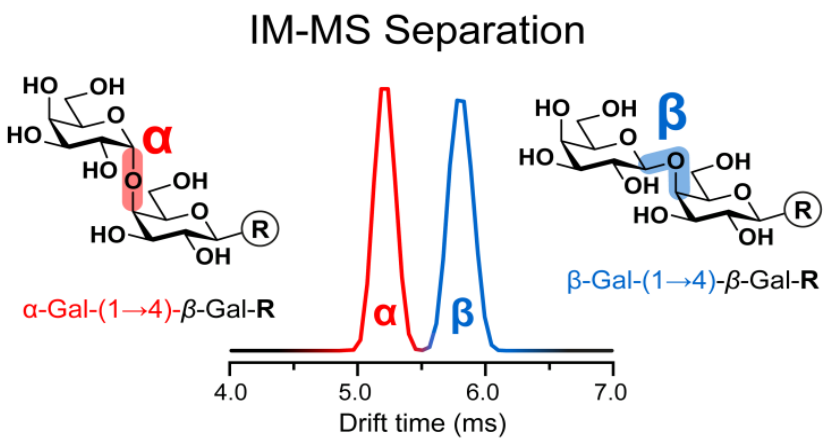
IMMS: Ion Mobility Mass Spectroscopy

- 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



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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

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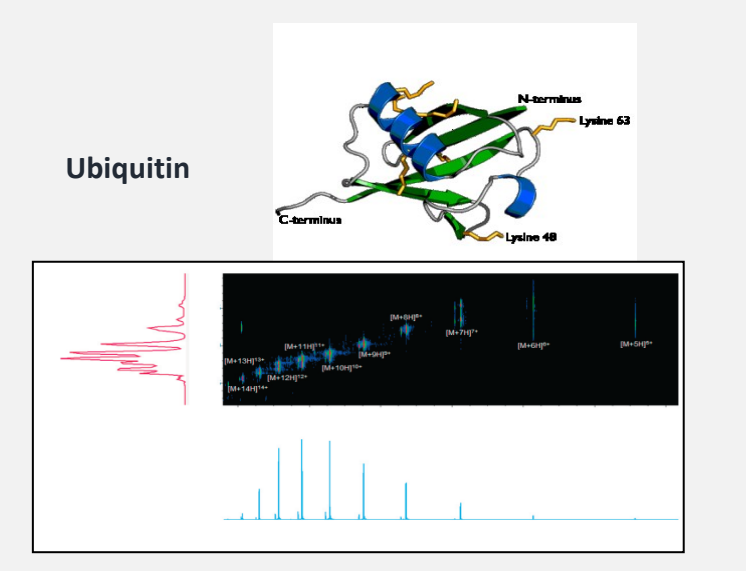
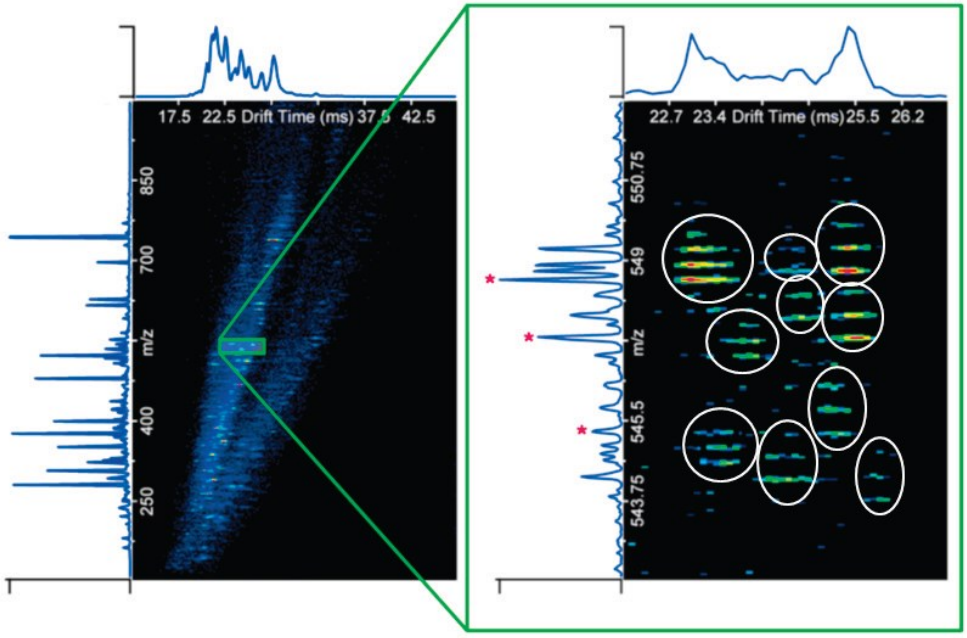
IMMS: Ion Mobility Mass Spectroscopy

- 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.





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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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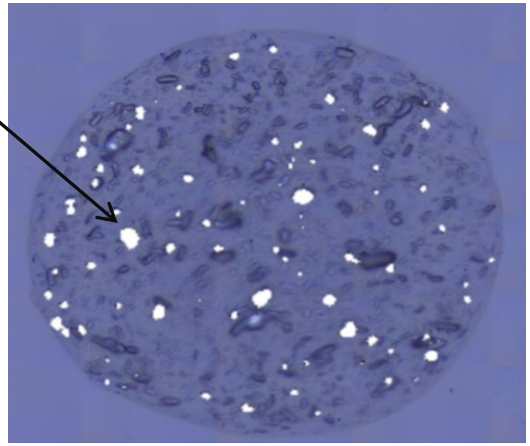
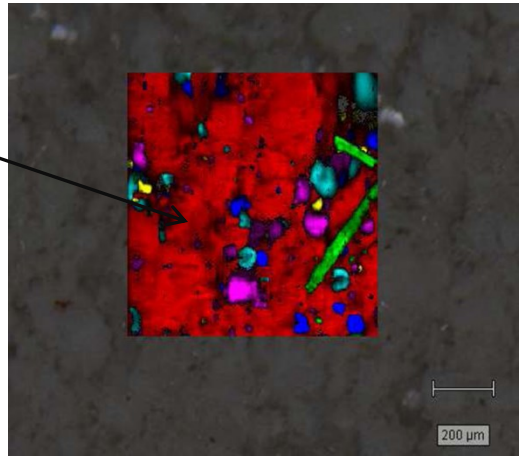
Micro-Raman Spectroscopy in Pharmaceutical Drug Developments

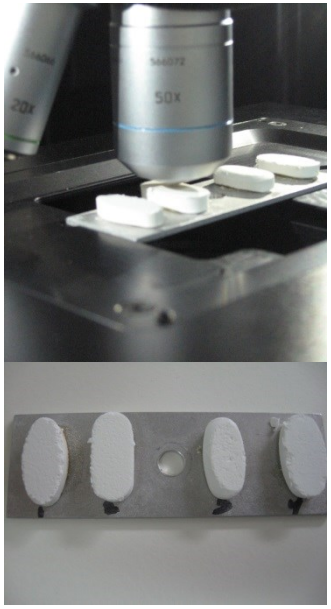
- Sharp spectral features
- Sensitive to solid state characteristics
- Sensitive to polymorphic forms
- The chemical finger print allow identification of DS in final products matrix
- Raman imaging and mapping allow obtaining the DS particle size in final products
- Relatively insensitive to water
- Little or no sample prep required
- Permits acquisition of the spectra in situ down to spot size of 0.5 microns
- Can be measured irrespective of the state of substance
- Applicable for biopharmaceutical samples such as proteins and more

DS PSD in final matrix



Formulation characterization in final product matrix





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Recruitment

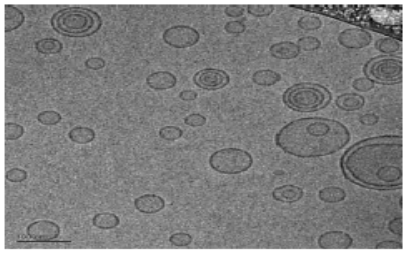
ESR3: Oral nano delivery – Formulation design and characterization

Job position advertised on:
EURAXESS: Job Offer ID: 325162
Teva's Global Analytical R&D Forum

- Number of Applicants: **22**
- Applicants Interviewed: 3
- Name of selected researcher: **Krishna Vippala**
- Contract start date: pending on TAU reply
- Contract end date: pending on TAU reply

ESR 3 - TEVA	Oral nano delivery – Formulation design and characterization	PhD: Yes	Deliv.: 3.2, 3.3	Start date: M6	Duration 36	WP3

Objectives: **1.** Develop an oral nano-delivery formulation; **2.** In-vitro characterization of the obtained system via different spectroscopies, such as SAXS, SLS and TEM; **3.** Large-scale GMP manufacturing of an oral formulation



Description: The emerging field of nanotechnology seeks to exploit distinct technological advantages of nanoscience. It is not only about the realization of devices, constructs, methods, and techniques at this size scale, but also about the functional enhancement gains over conventional technology. Although development of an oral-nano formulation is very challenging, it serves as an unmet need, which we would like to address. Nanoparticles (NPs) formation represents a significant industrial challenge because of the physical limitation for sub-micron sizing, physicochemical stability, purity, and concerns about the large-scale cGMP-compliant manufacturing of such products. TEVA has the capabilities and the experience in moving a product from the academy to the market, finding the best formulation, which will exhibit improved pharmacokinetic profile and reduced toxicity. *In-vitro* and *in-vivo* characterization of the NPs will help us better understand our systems and find the best candidate for scale-up manufacturing.

Planned secondments: IBEC – NP imaging (M18, 4 months); **TUE** – SAXS characterization of NP (M30, 3 months).	**Expected results (deliverables)**: Development of lipid/polymer-based nano formulation in lab scale (D3.2); Extensive physicochemical characterization of the NPs (D3.3); NPs GMP Manufacturing in larger scale (scale-up) (D3.2)

Teva Supervisor: **Dr. Bianca Avramovitch**
TAU Supervisor**: Prof. Roey Amir**

Recruitment incomplete

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Recruitment

Main experienced hurdles which delayed our ESR hiring up to today:

1. Visa and accordingly budget
2. Bureaucracy with TAU

1. Issuing a visa for our ESR:

- Different visa requirements for academy and industry
- The B1 expert visa is the mandatory one
- B1 expert visa for industry requires very high month salary (2.5 times of avg.), therefore, the consortium budget did not cover the expenses
- Neither Teva or the Israeli MoI knew there is a special category in the B1 visa for Horizon2020 researchers, with adjusted salary requirements
- This special category fits within the consortium budget
- Numerous bureaucracy hurdles were encountered as MoI didn't know how to instruct us and it turned out that we taught them the relevant procedure
- Only now (March 18) the correct visa permit was approved

2. Bureaucracy with TAU

- The scientific collaboration between Teva and TAU is very good
- Our ESR was accepted to TAU as a PhD student with the following constrains:
  - Formal doctoral supervision cannot be from the industry. Supervisor will be from TAU (Roey Amir) and the work will be conducted at Teva's facilities with Bianca Avramovitch as an advisor - ***agreed***
  - Teva and TAU must sign an additional agreement between them - ***still open***

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Planned Research Activities and Deliverables

Planned research for Teva ESR 3 – first stage :

- To synthesize enzyme-responsive hydrophobic dendrons according to procedures developed by Prof. Amir (TAU) and to modify it to target the specific indication
- To develop high resolving methods for characterizing the species developed in collaboration with TAU and any other interested consortium partners
- To develop methods which should monitor the processes involved and researched
- To evaluate the new species in biological systems
- The ESR will be trained and certified on the main technologies in use for characterization of the different required matrixes:
  - IMMS (ion mobility mass spectrometry), CE (capillary electrophoresis)
  - Micro Raman, Micro CT, Micro FTIR, SEM-EDX
  - Particles imaging, with size and shape distribution, by various laser diffraction instruments (QicPic, Morphologi GI, Mastersizer)
  - MALLS (multi angle laser light scattering)

Planned research for Teva ESR 3 – second stage deliverables:

- Development of lipid/polymer-based nano formulation in lab scale (D1.2)
- Extensive physicochemical characterization of the NPs (D1.3)
- NPs GMP Manufacturing in larger scale (scale-up) – depending on the previous steps success (D1.2)

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Planned secondments:

At Teva :

- **ESR 4 – TUE** – industrial formulation of SCPN (M30, 3 months)
- **ESR 10 – BAS** - encapsulate catalyst in lipid NP (M36, 3 months)
- **ESR 13 – TAU** (Satchi Fainaro) – oral formulations (M36, 3 months)

ESR 3 - TEVA.

- **At IBEC**: NP imaging (Month 18 – 21, 4 months)
- **At TUE** – SAXS characterization of NP (Month 30, 3months)

Planned Trainings:

Sept 26, 2019, Basel

How can we do better in bringing new molecules to the market: scaling up, formulations, regulations, procedures and economical aspects	TEVA (B.Avramovitch)	SCI COMP	1 day

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Update on Teva IP Activities and Committee

3.2.6 Intellectual Property Rights (IPR)

The IP and innovation committee (led by TEVA) will be responsible to supervise the activity of the consortium to find potential marketable occasions. The IP and innovation committee will be in touch with the local tech transfer offices to manage the strategy for successful translation of the know-how generated in the consortium into marketable products. The beneficiary or beneficiaries responsible for the new technology will own the IP and will have to responsibility to patent it and exploit it. In case of joint IP or IP generated during secondments the involved beneficiaries will sign an agreement on IP exploitation. All beneficiaries will be allowed to access the research results for research or training purposes. IPR regulations will be detailed in the consortium agreement between beneficiaries and partners and serve as a reference. If required secondments, meeting or results sharing will be performed under a non-disclosure agreement. However, attention will be dedicated in order to do not prevent the possibility of publication of the ESRs.

IP and Innovation Committee:

- Dr. Bianca Avramovitch – TEVA
- Dr. Marc Robillard – TAG
- Dr. Asier Unciti - Brocheta – EDI

Action Items:

1. Build a mechanism of teams reporting to the committee the “know-how” generated in their own research teams
2. Identify the potential marketable occasions
3. Manage the strategy to patent and share the IP