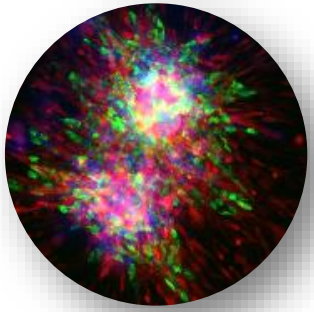
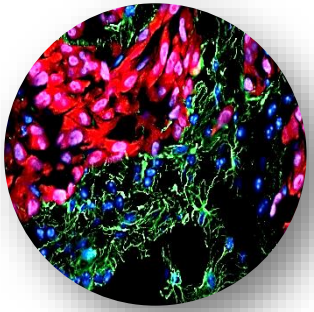
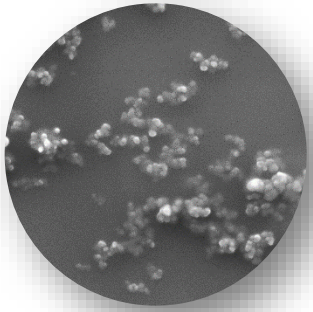
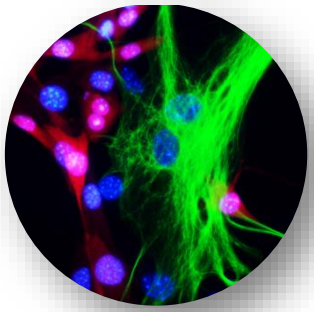
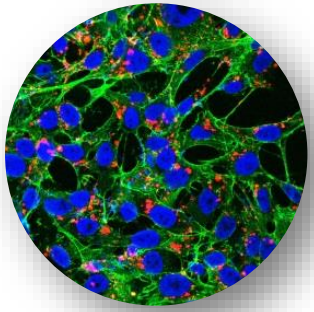
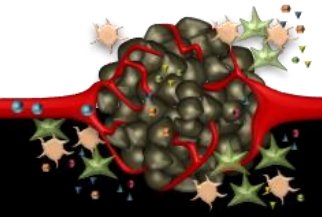
# *Cancer Theranostics in three dimensions*

***THERACAT Mtg, Eindhoven***
***26th March 2019***



**Prof. Ronit Satchi-Fainaro, Ph.D.**
**Head, Cancer Research and Nanomedicine Laboratory**
**Chair, Department of Physiology and Pharmacology**
**Chair, The Lion Cathedra in Nanosciences and Nanotechnologies**
**Sackler Faculty of Medicine, Tel Aviv University, Israel**

TEL AVIV UNIVERSITY
Pursuing the Unknown

Be Part of the Next Big Idea – TAU Global Campaign

# TAU Overview

- TAU is Israel's largest and most comprehensive research and teaching university: 9 Faculties, 125 Departments, 130 Research Institutes and 17 affiliated hospitals
- 30,000 students: 14,000 are Master's and Doctoral Candidates
  Over 1,200 International Students Per Year from More Than 60 Countries
- TAU is consistently ranked in the top 20 in the world in terms of scientific citations and among the top 100 universities in the world in terms of research impact
- Tel Aviv University among top 10 in the world for producing VC-backed entrepreneurs

TEL AVIV UNIVERSITY
Pursuing the Unknown

Be Part of the Next Big Idea – TAU Global Campaign

# TAU Overview

- Through “RAMOT” – TAU Technology Transfer company:
  2,400 patents filed to date, 65 spinoff companies generated, over 180 license and option agreements concluded

- Tel Aviv University is ranked 48th in the world in receiving U.S. patents with 54 patents granted in 2016. The National Academy of Inventors (NAI) report ranks TAU above all other academic institutions in Israel and places it 8th among institutions outside the United States.

- 23 drugs and medical therapies being developed right now

**Sackler Faculty of Medicine**
Tel Aviv University

- Israel's largest medical research and training complex
- Basic and translational research conducted in 125 laboratories on TAU campus and 17 affiliated hospitals

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Sackler Faculty of Medicine
Tel Aviv University

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# Sackler Faculty of Medicine by the numbers

125 Preclinical Faculty members
1500 Clinical Faculty members from 17 affiliated hospitals

More than 2800 graduate, dental & medical students

Education
MSc, PhD & MD degrees

International MSc & PhD program

Research Revenue
$40.7M total research revenue 2017-2018

Sackler Faculty of Medicine
Tel Aviv University

TEL AVIV UNIVERSITY
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# Research Cores & Centers

- Genomic Analysis Laboratory
- Single Cell Analysis Core
- Neuro-Behavioral Core Facility
- Virus Core Facility
- Cellular and Molecular Imaging Center
- SPF Building for Transgenic Modeling of Human Disease
- SPARK, Center for Translational Medicine
- TAU Cancer Biology Research Center
- Safra Center for Bioinformatics
- TAU Center for Nanoscience & Nanotechnology
- Blavatnik Center for Drug Discovery

SICF
Sackler Interdepartmental Core Facility

GAL
Genomic Analysis Lab

The Myers Neuro-Behavioral Core Facility

BLAVATNIK CENTER for Drug Discovery
מרכז בלווטניק לפיתוח תרופות

TEL AVIV UNIVERSITY
אוניברסיטת תל אביב

# Prof. Ronit Satchi-Fainaro, Ph.D.

TEL AVIV UNIVERSITY אוניברסיטת תל אביב

RSF Lab

http://medicine.mytau.org/satchi-fainaro

**Present:**

***Full Professor,*** Sackler Faculty of Medicine, Tel Aviv University.
***Head***, Cancer Research and Nanomedicine Laboratory
***Chair***, The Hermann and Kurt Lion Cathedra in Nanosciences and Nanotechnologies
***Member***, Board of Governors, Tel Aviv University
***Director***, Board of Directors, Teva Pharmaceutical Industries Ltd.

**Past education:**

***Postdoctoral Associate***, Harvard Medical School. **PI: Judah Folkman**
***Ph.D.,*** University of London, UK. **PI: Ruth Duncan**
***B.Pharm.,*** The Hebrew University of Jerusalem, israel.

**Past positions**:

***President,*** The Israeli Controlled Release Society (CRS) (2010-2015)
***Chair*** , IACUC of Tel Aviv University (2013-2017)
***Chair***, Department of Physiology and Pharmacology (2014-2018)

**Selected Honors & Awards:**

| | |
|---|---|
| **2006** | EACR Young Investigator Award. |
| **2006-2009** | Alon Fellowship for Outstanding Young Investigators. |
| **2010** | The JULUDAN Prize for the Advancement of Technology in Medicine. |
| **2013** | Teva Pharmaceutical Industries Founders Award. |
| **2009-2019** | Included in several 50 most promising and influential people (Forbes, Globes, 40 under 40 TheMarker, Calcalist). |
| **2016** | Israeli representative at the Biennale in Venice, Italy, on the Inspiration of Biology and Medicine on Architecture. |

**Scientific Advisory boards:**

Blavatnik Center for Drug Discovery, the Israel Cancer Association, the Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR, Barcelona, Spain), VLX (VC) and several Editorial Boards of Scientific Journals.

**Research projects in the lab:**

1. Three-dimensional cancer models (murine, human, PDX);
2. Nanovaccines for cancer immunotherapy;
3. RNAi delivery

**Publications:** 110; **H-Index:** 38; **Books:** 12; **Citations:** 6000; **Patents:** 51 (licensed technologies to Merck, Biosynth, Vectura); **PCs:** >60; **Grants:** €18M (since independent position); **Current research associates, students, postdocs and technicians:** 30; **Invited Lectures:** >350

erc · Melanoma Research Alliance · MERCK · Khan Foundation · ICRF Israel Cancer Research Fund · Israel Science Foundation · EuroNanoMed2 · European Training Network THERACAT

## Tel Aviv University (TAU)-ESR 13

## Daniel Rodriguez, PhD student (Dec 2018- todate)

Responsible for the **biological evaluation on cancer models**
**Secondments, collaborations and training** at IBEC (LA), TU/e (LA), BioGelX, Teva (BA), TAU (RA)
Organize a **workshop at TAU** on Year 3

# Mechanisms of molecular and cellular tumor-host interactions underlying tumor dormancy

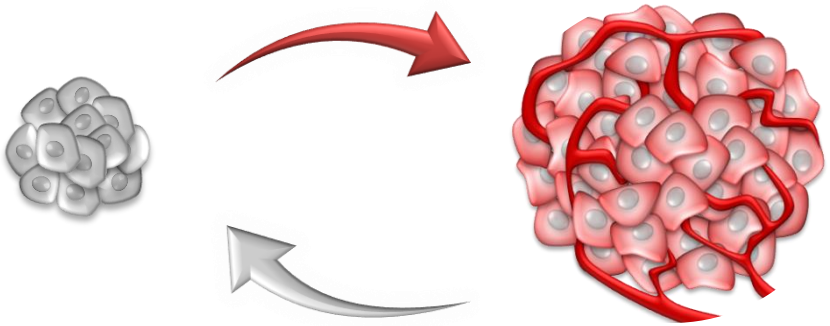
1. What are the basic mechanisms that MAINTAIN the state of tumor dormancy?

2. What are the events that INITIATE the transition from dormancy to progressive disease?

3. Is this transition REVERSIBLE?

4. Can we define and understand the mechanisms used by CANCER CELLS TO HIJACK THE FUNCTIONS OF NORMAL HOST CELLS ?

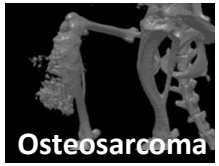
5. Can we apply this knowledge to sensitively DETECT AND TREAT cancer by disrupting these tumor-host interactions?

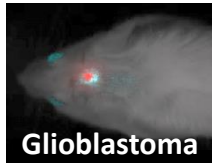


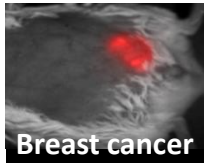
# Research approach

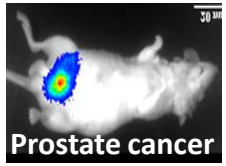
## Animal model (Human & Murine)

Primary *vs.* Metastatic • Dormant *vs.* Fast-growing • Drug sensitive *vs.* Resistant



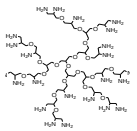




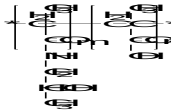



## Polymeric nanocarrier

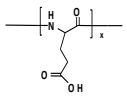
PG-Amine dendrimer



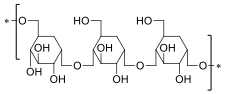
HPMA copolymer



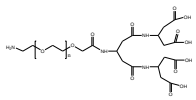
PGA



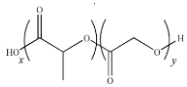
Pullulan



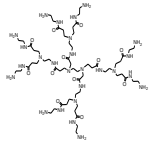
PEG-PGA dendron



PLGA

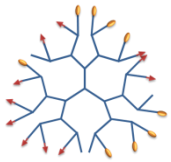


PEI-PAMAM dendrimer

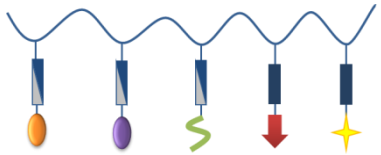


## Supra-molecular structure

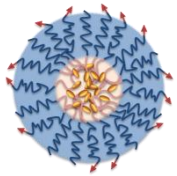
Dendritic



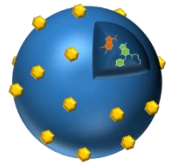
Linear-Hyperbranched



Micellar



Nanoparticle



## Targeting

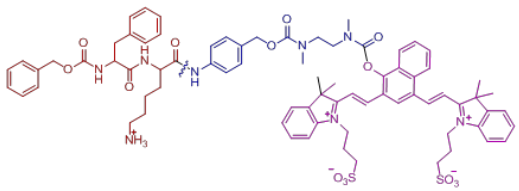
## Active entity

| Alendronate | Folic acid | RGD PM / TSP-1 PM | NCAM | Nestin |
|---|---|---|---|---|
| ↓ | ↓ | ↓ | ↓ | ↓ |
| Bone tumors | Folate receptor (tumor cells) | Integrin αvβ3, αvβ1 (tumor endothelium) | Tumor initiating cells | Brain tumors |

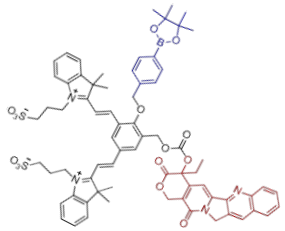
**siRNA/miRNA** **Antigens/Neo-Antigens** **TNP-470** **MEKi** **BRAFi** **Paclitaxel** **Temozolomide** **Doxorubicin**

## Turn-ON Theranostic Probes

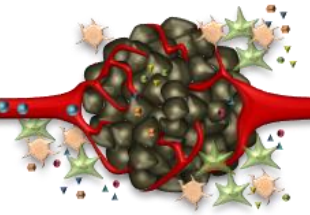
Enzyme-based probe →



Analyte-based probe →



# Nanomedicine co-targeting of neuroinflammation in melanoma brain metastasis



Model

OMICs

Proteome profiler

Mutation sequencing

Function

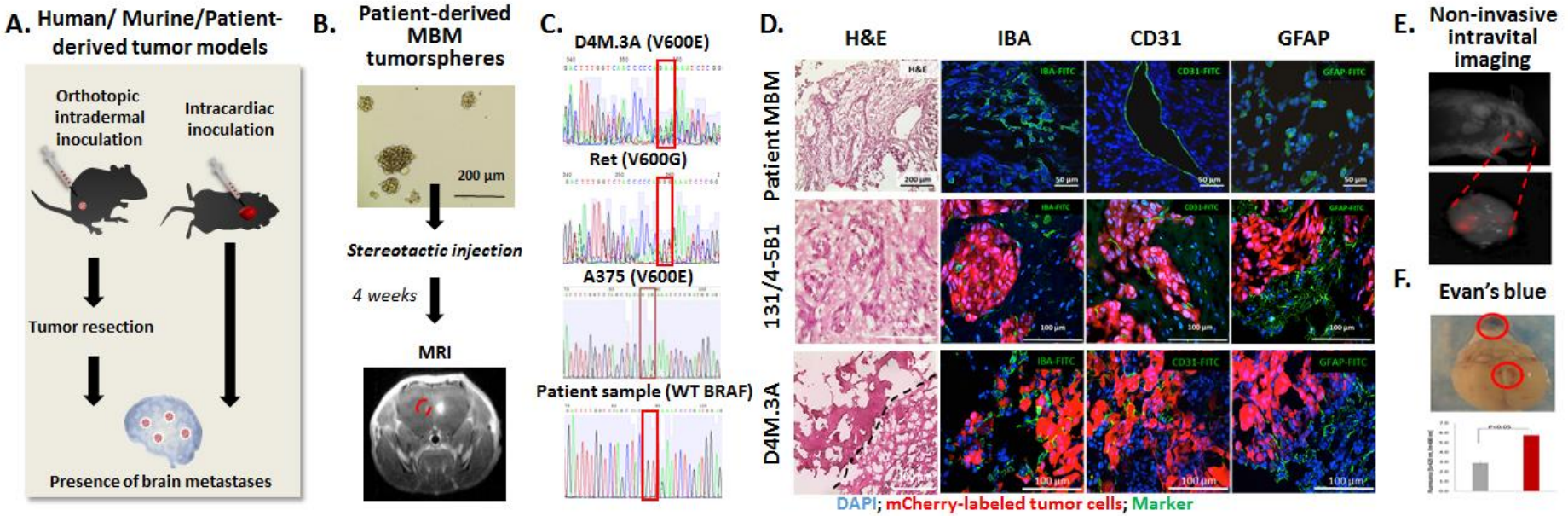
Precision Nano-medicines

MEK inhibitor

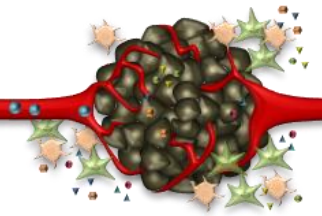
BRAF inhibitor

Preclinical Studies

# Micro- and macro-metastases appearance in a murine, human and PDX mouse models of melanoma brain metastases



# Research approach: melanoma as a model



Patient with melanoma

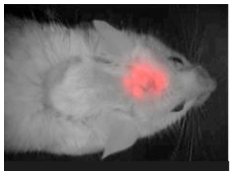
Histology

FFPE specimens (IHC, ISH, RNA)

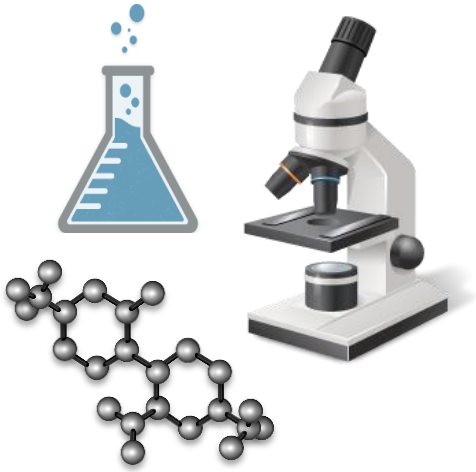
Cell lines

3D printer

Mouse models



Target discovery & Drug design

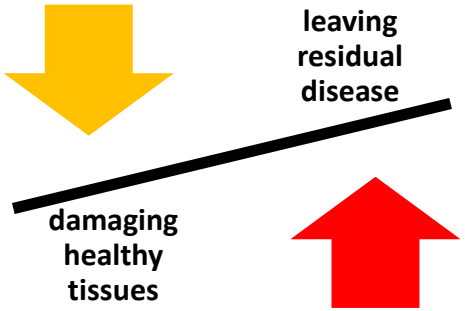


# Turn-ON nanoprobes illuminate tumors during image-guided surgery leading to prolonged survival

1. Complete excision of tumors is crucial for reducing the risk of the disease recurrence

2. Surgeons should leave no residual cancer cells after surgery

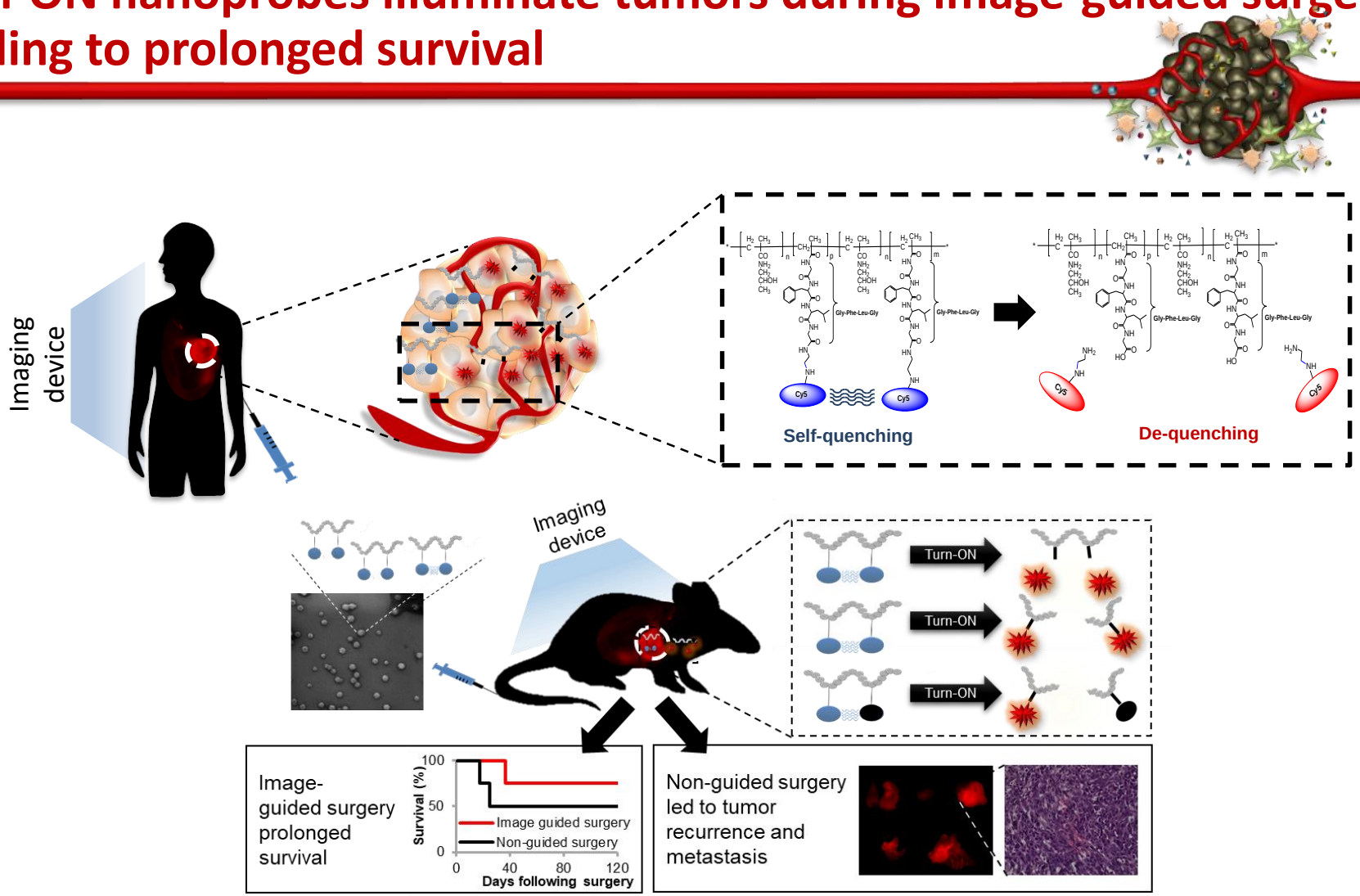
3. There is a need to clearly mark the tumor boundaries





Blau*, Epshtein*, Pisarevsky* *et al.* 2018, *Theranostics*,, (13): 3437-3460 (2018)

# Turn-ON nanoprobes illuminate tumors during image-guided surgery leading to prolonged survival





Blau*, Epshtein*, Pisarevsky* *et al.* 2018, *Theranostics*,, (13): 3437-3460 (2018).

Weinstain, *et al., Chemical Comm.*, 46(4):553-5 (2010)

Karton-Lifshin , *et al., JACS,* 133(28), 10960-10965 (2011)

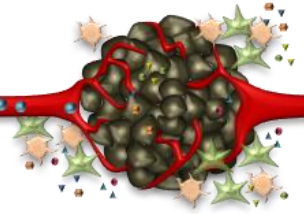
Redy, *et al*., *Nature Protocols*, 9(1) 27-36 (2014)

Kisin-Finfer, et al., Bioorg Med Chem Lett, 24(11) 2453-8 (2014)

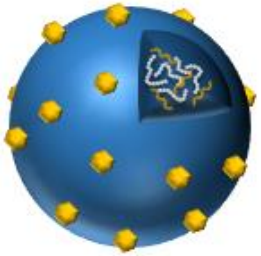
Ferber, *et al. JoVE,* Nov 23;(93):e51525 (2014)

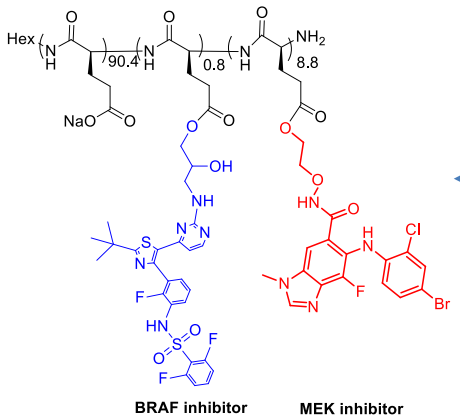
Ferber, Baabur-Cohen, Blau *et al*., *Cancer Letters* 352(1):81-9 (2014)

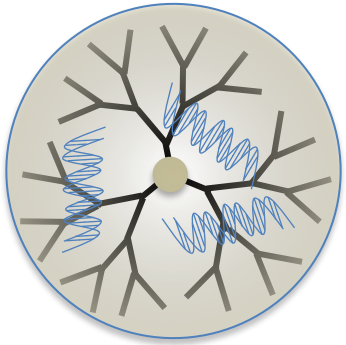
# Rational design of precision nanomedicines for prevention, intervention and regression of melanoma brain metastases



**Prevention** ⟷ **Intervention** ⟷ **Regression**





**Mannose-PLGA MART-1 nano-vaccine**

**Conniot, Scomparin, Florindo, Satchi-Fainaro**

**PGA-BRAFi-MEKi nanoconjugate**

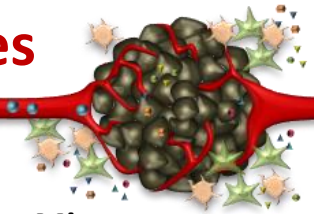
**PLGA-BRAFi-MEKi Nanoparticle**

**Pisarevsky, Epshtein, Scomparin, Koshrovsky, Conniot, Florindo, Satchi-Fainaro**

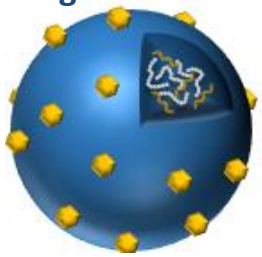
**PGA-cytokine siRNA nanopolyplexes**

**Pozzi, Ben-Shushan, Eldar-Boock, Scomparin, Krivitsky, Eliyahu, Satchi-Fainaro**

# Melanoma brain metastasis – targeting opportunities

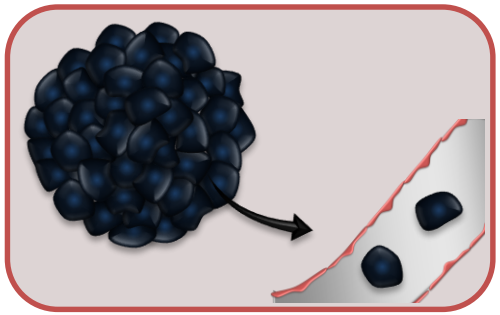


Targeting Dendritic cells

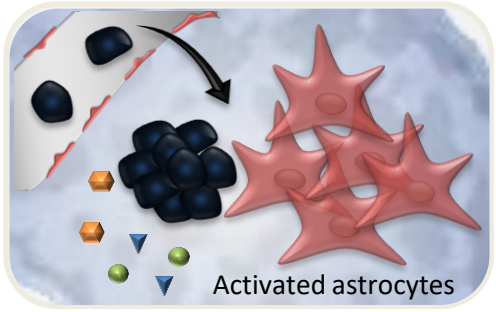


Primary melanoma tumor

1

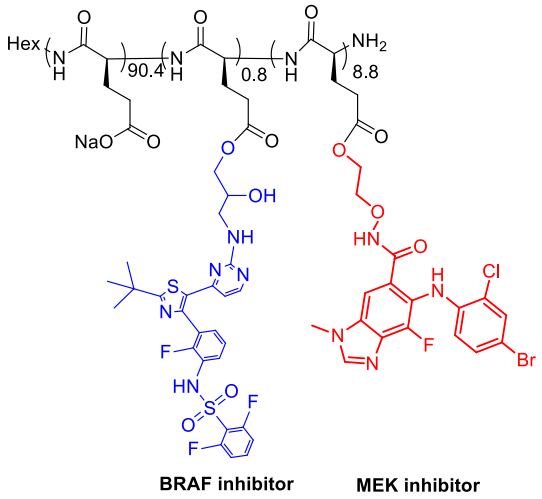


Micrometastases establishment



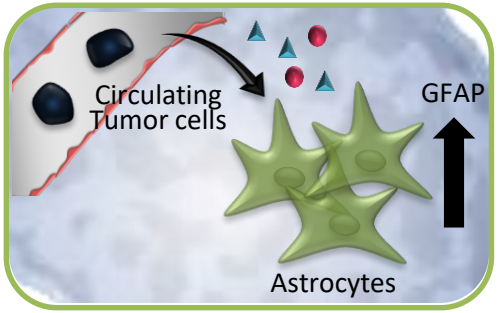

6

Targeting melanoma cells

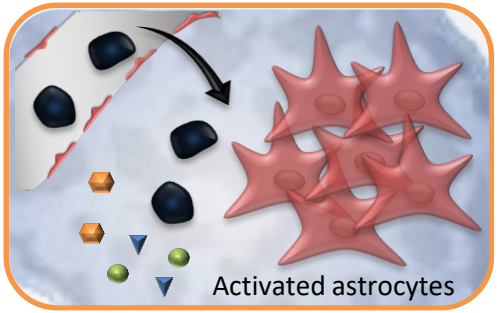



Astrocytes activation (increased GFAP)

2

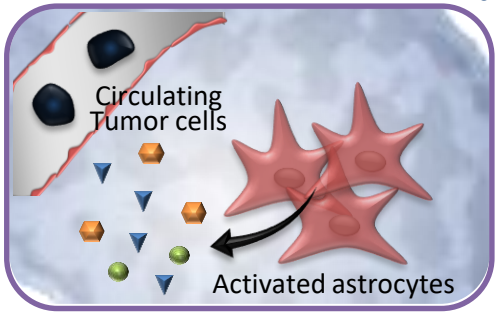



Extravasation of melanoma cells through the leaky vessels



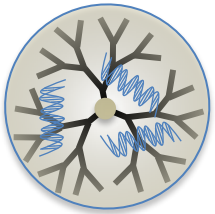

5

Cytokine secretion

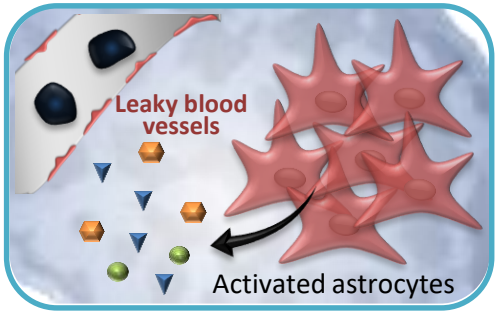



3

Targeting cytokine secretion using siRNA nanocarriers



Astrogliosis and neuroinflammation




4

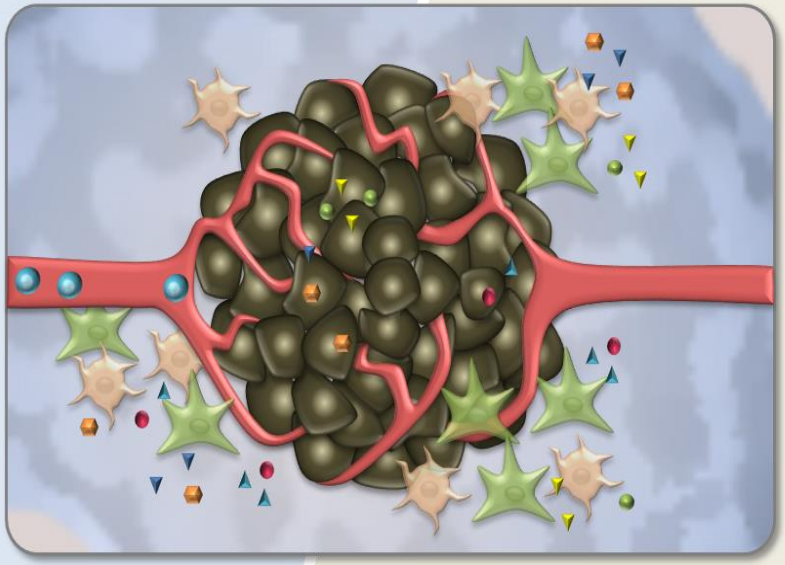
# From Bench to bedside and back

Bedside

Bench

Patient with brain metastases

3D-printed brain metastases model



Precision nanomedicines

**Prevention**

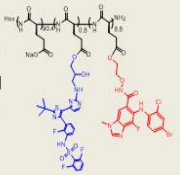
Activating T cells against cancer-specific antigens by nano-vaccines

**Intervention**

Targeting cytokine secretion by siRNA nano-polyplexes

**Regression**

Targeting cancer cells by precision nano-conjugates



**3DBrainStrom: Bridging the translational gap - bedside to bench and back**

# RSF's Multidisciplinary research team

## *The whole is greater than the sum of its parts …*

### Biology

Establishment and molecular characterization of pairs of dormant vs fast-growing, primary vs metastatic and resistant vs drug-sensitive orthtopic tumor models

**Paula Ofek, PhD**
**Dikla Ben-Shushan, PhD**
**Anat Eldar-Boock, PhD**
**Galia Tiram, PhD**
Shiran Ferber, PhD
**Hadas Gibori, PhD**
**Eilam Yeini**
**Sabina Pozzi**
**Noa Reisman**
**Sapir Golan**
**Sahar Dangor**
**Roni Blatt**
**Yael Shtilerman**
Keren Miller, PhD
Liron Stern
Christian Burgos

### Medicine

Patient-derived tumor models

**Rachely Grossman, MD**
Natav Hendin, MD student
Adi Hirschhorn, MD student
**Miki Goldenfeld, MD student**
Shelly Sofer, MD student
Roni Shreberk-Atidim, MD
Ilanit Shetzigovski-Meller, MD
Gal Bachar, M.D.

### Engineering

3D tumor models

**Lena Neufeld**
Tal Zur
Zohar Shatsberg
Ehud Segal, PhD
Liora Omer

### Chemistry

Design, synthesis and characterization of 20 novel nanomedicines

**Anna Scomparin, PhD**
Shay Eliyahu, PhD
Hemda Baabur-Cohen , PhD
Ela Markovsky, PhD
Dina Polyak, PhD
**Adva Krivitsky, PhD**
**Racheli Blau**
**Yana Epshtein**
**Yevgeny Pisarevsky**
**Joao Conniot, PhD**
**Shani Koshrovski**
**Alessio Malfanti, PhD**
**Ruri Ruperti**

**Administration**

**Ayelet Hashdi**