A Liquid Biopsy ‘hub’: integrating nano-technologies to improve cancer diagnosis and therapy

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Liquid biopsy, nanotechnology, precision cancer diagnosis, nanotherapy

**Liquid Biopsy**
- Predicting outcome by LB (lead time)
- Discovery adaptive resistance to clinical HER2 blockade
- Assign target therapy based on LB
- Moving liquid biopsy into nanophotonics

**GIM21 multi-center**

**TOOLBOX stepwise**

**Molecular Tumor Board**

**- Standard of Care**
**- Real-Life trials**

**- Beyond Standard of Care**

https://www.oncotech.org/gim21
Liquid Biopsy
Monitoring T-DM1 treated patients by liquid biopsy

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Paolo Romania
Francesco Cognetti
Michelangelo Russillo
Gianluigi Ferretti
Simonetta Buglioni
Edoardo Pescarmona

Trastuzumab -emtansine (T-DM1)
ADC

TTZ/PTZ + taxanes etc
Cycle 1 T-DM1
Cycle 2 T-DM1
Cycle 3 T-DM1
Cycle n T-DM1

relapse
progression

pt#1 age 54
Progression by ctDNA
Progression by PET
Blood drawings
Lead time: 2.1 months
primary resistance

pt#2 age 59
Progression by ctDNA
Progression by CT scan
Blood drawings
Lead time: 2.8 months
adaptive resistance

pt#3 age 38
Progression by ctDNA
Progression by PET
Blood drawings
Lead time: 0.9 months
Long response

pt#7 age 52
Progression by ctDNA
Progression by PET
Blood drawings
Lead time: 2.9 months
response + adaptive resistance

Alegretti, M. … and Fabi, A. 2019, in preparation
**Liquid biopsy reveals new vulnerabilities not present in archival tumor tissues**

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<th>Plasma behaviour (ctDNA)</th>
<th>Actionable (OncoKB level ≤3)</th>
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**IRE Molecular Tumor Board**
- Hematologist
- Surgeon
- Nurse
- Pharmacologist
- Medical Oncologist
- Pathologist
- Biostatistician
- Molecular Biologist

**Notes:**
- Pts w/actionable SNVs on progression 5/8 (62.5%)  
- Tumor vulnerabilities only seen in blood  
- Tumor vulnerabilities not present at the beginning of T-DM1 treatment
Liquid Biopsy by Nanophotonics
ULTRAPLACAD: ULTRA-sensitive PLAsmonic CAncer Diagnosis

Since October 24th 2018 a compact plasmonic industrial prototype is installed at IRE.

www.ultraplacad.eu

EU H2020 Grant no: 633937
Nano-therapy
TOOLBOX: modular objects for step-wise nano-therapy

1. Strep-Tagged huW6/800 to HER2
2. Strep Tactin multimer
3. Strep-Tagged drugs (e.g. DM1)
4. Strep-Tagged HLA-A2 tetramer

HER2 breast cancer

Joachim Bertram
Karl Heinz Friedrich
Leonardo Sibilio
Loredana Cecchetelli

(5-10 nm)
H-nanoferritin (HFT): cage and carrier for antiblastic payloads

- Ferritin is a natural non-toxic protein selected during evolution to be stable in body fluids and pass body barriers.
- Made of 24 subunits (H and L chains), it is produced in recombinant form as HFT (24 heavy chains).
- HFT (heavy chains only) is produced in high yields (5 g/L) in E. Coli, it is stable at 75 °C and at pH=2.0.
- HFT entraps more drug molecules inside its cavity (30-200 mol depending on the drug) as compared to albumin (HSA) or ADCs.
- HFT is actively uptaken through its natural receptor (CD71, the transferrin receptor). This is adaptively over-expressed (10-100 fold) in cancer cells.
Recombinant HFt in vivo

1. Innovative industrial process
   - Bacteria 5g/L
   - Autoassembly
   - Double drug loading surface
   - Up to >100 drugs/molecule
   - Shelf-life
   - Lyophilization

2. Wide Drug nano-caging spectrum
   - Cisplatin
   - Doxorubicin
   - Doxorubicin analogues
   - MMAE
   - Mitoxantrone
   - Topoisomerase inhibitors

3. Wide spectrum of potential tumor targets
   - Pancreas adenocarcinoma
   - Melanoma
   - Breast Carcinoma 3N
   - Sarcoma
   - Colorectal Carcinoma
   - Head & Neck

4. Favorable PK

5. Therapeutic efficacy

6. derivatization

Ferritin mAb post-synthesis & recombinant
A Liquid Biopsy ‘hub’: integrating nano-technologies to improve cancer diagnosis and therapy: conclusions

- Drug resistance
- Loss of target

 Genome-driven, modular personalized medicine

 Cycle 1
 Cycle 2
 Cycle 3
 Cycle n

 LB-guided combination targeting

 Combination drugging

 ctDNA

 CD71
 HER2
Acknowledgements and disclosure of potential conflicts of interest

main academic partners

Consiglio Nazionale delle Ricerche
Università degli Studi di Catania
Sapienza Università di Roma
Universitäts Klinikum Jena
Istituto Nazionale Tumori Regina Elena

non-profit support

• H2020 RIA and MSCA
• Lazioinnova
Eureka E!5995

main industrial partners

IBI
Thena Biotech
Roche

recent patents

EP3186192B1
WO2017167967A1
WO2018138676A1
A ‘Precision Oncology open day’

- To be held in Rome Q1 2020.
- Co-supported and co-sponsored by the ICPerMed recognition prize award
- The purpose will be to raise awareness about the new mutational oncology model and the precision oncology potential
- Target audience: specialists and non-specialists, e.g. surgeons, medical oncologists, radiologists, pathologists etc, science writers and journalists, patients and patient advocacy organizations, entrepreuners, the general public, policy makers and the Italian and EU Institutions
- Short introductory talks for both specialists and non-specialists about genome-driven oncology, its tools (molecular diagnosis report, the Molecular Tumor Board, off-label treatment), and relevant financial, regulatory, deontological, and ethical issues
- Duet-talks by patients and their physicians: exceptional responders, liquid biopsy therapy assignee, Lazarus responders etc seen by the Regina Elena MTB.

Final agenda to be assembled: ICPerMed, the Italian Ministry of Health, and the local Health Authorities in Rome