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SfR 6







Precision medicine today : targeting unique cellular pathways for treating patients

Cibler des voies cellulaires uniques pour une médecine de précision

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### Precision Medicine

Médecine de precision en cancérologie: Une approche émergente de thérapie anticancéreuse fondée sur le profil une d'une tumeur donnée **Precision medicine (PM)** is an emerging approach that aims to tailor therapeutic strategies for cancer based on the individual's tumor unique profile

#### **Traditional Medicine vs. Precision Medicine**



Genetics Immunotherapy Targeted therapies

# Most chemotherapeutic approaches were aiming to eliminate rapidly cycling cells



- Taxol
- Cisplatin
- Anthracyclines
- Cytarabine
- Topoisomerase inhibitors

Damage to normal tissues Do not eliminate the cancer stem cells

# Tumors may have unique druggable mutational changes



lutated gene	<b>Common genetic alterations</b>	Tumors implicated	Drugs
LK	Mutation, fusion	Non-small cell lung cancer	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
TM	Mutation	Breast	Olaparib
SCR-ABL	Fusion	Chronic lymphocytic leukemia, acute lymphocytic leukemia	Bosutinib, dasatanib, imatinib, nilotinib, ponatinib, asciminib
BRAF	Mutation	Melanoma, colorectal, hairy cell leukemia, thyroid	Dabrafenib, encorafenib, vemurafenib, binimetinib, cobimetinib, trametinib
RCA1/2	Mutation	Breast, ovarian, prostate	Olaparib, niraparib, rucaparib, talazoparib
HEK2	Mutation	Breast, ovarian	Olaparib
SF1R	Mutation, fusion	Giant cell tumor	Pexidartinib, sunitinib <sup>A</sup>
GFR	Mutation, fusion, amplification	Non-small cell lung cancer	Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib, brigatinib <sup>A</sup> , amivantamab
RBB2/3/4	Amplification, mutation	Breast	Afatinib <sup>a</sup> , lapatinib, neratinib, tucatinib, trastuzumab <sup>B</sup> , pertuzumab <sup>B</sup> , margetuximab
ZH2	Mutation	Lymphoma	Tazemetostat
GFR1/2/3	Mutation, fusion	Cholangiocarcinoma	Erdafitinib, lenvatinib <sup>4</sup> , pemigatinib, infigratinib
TLT3	Mutation	Myeloid leukemia	Gilteritinib, midostaurin, sorafenib <sup>A</sup>
DH1/2	Mutation	Myeloid leukemia, cholangiocarcinoma, glioblastoma	lvosidenib, enasidenib
4 <i>K2</i>	Mutation	Myeloproliferative syndrome	Fedratinib, ruxolitinib
(17	Mutation, fusion	Gastrointestinal stromal tumor, mastocytosis, melanoma	Avapritinib, imatinib, pazopanib <sup>A</sup> , pexidartinib <sup>A</sup> , ripretinib, sorafenib, nilotinib <sup>A</sup> , sunitinib
(RAS	Mutation	Non-small cell lung cancer	Sotorasib
1ET	Mutation, fusion	Non-small cell lung cancer	Cabozantinib <sup>A</sup> , capmatinib, crizotinib <sup>A</sup> , tepotinib
ITRK	Fusion	Many solid tumors at low frequency	Larotrectinib, entrectinib
PDGFRA/B	Mutation, fusion	Gastrointestinal stromal tumor, mastocytosis, hypereosinophilic syndrome	Avapritinib, imatinib <sup>a</sup> , sorafenib <sup>a</sup> , sunitinib <sup>a</sup> , lenvatinib <sup>a</sup> , pazopanib <sup>a</sup> , ripretinib <sup>a</sup>
РІКЗСА	Mutation	Breast	Umbralisib <sup>A</sup> , duvelisib <sup>A</sup> , idelalisib <sup>A</sup> , copanlisib <sup>A</sup> , alpelisib, temsirolimus <sup>A</sup> , everolimus <sup>A</sup>
ML-RARA	Fusion	Myeloid leukemia	Arsenic trioxide, retinoic acid
RET	Mutation, fusion	Renal, thyroid, non-small cell lung cancer	Pralsetinib, selpercatinib, cabozantinib <sup>A</sup>
2051	Fusion	Non-small cell lung cancer	Entrectinib, crizotinib
MO/PTCH1	Mutation	Medulloblastoma, basal cell carcinoma	Vismodegib

<sup>A</sup>Mutation-specific treatment supported by National Comprehensive Cancer Network guidelines that does not have full FDA approval. <sup>B</sup>Base antibody used alone or as antibody-drug conjugate. J Clin Invest DOI: 10.1172/JCI154943

## Tumors may express unique surface molecules



- Monoclonal antibodies
- Antibody-Drug conjugates
- Bi-Specific antibodies
- Chimeric antigen receptor T cells
- Chimeric antigen receptor NK cells

### **CART cell therapy**



- Engineered receptors to target surface molecules
- Allows MHC-independent antigen recognition
- Engagement via single-chain variable fragment (scFv)
- T-cells replicate in response to contact with antigen

### **Approved CAR T cell products**



### Allogeneic CART cell process



### Targeting CD123 with Allogeneic TCR $\alpha/\beta$ Deficient CAR T-Cells



#### **UCART123** attributes

- Anti-CD123 scFv
- 2nd Generation CAR:

4-1BB + CD3z

- TCR $\alpha\beta$  knock-out using TALEN<sup>®</sup> Gene Editing (TRAC KO)
- Safety feature: RQR8 + (renders cells sensitive to rituximab)

*T-cells were generated and provided by Cellectis SA* 

### Primary derived xenotransplants (PDX) were generated to test in vivo activity of UCART123





Schematic created with biorender.com

### Challenges

- How to assess MRD?
- How to monitor CART cells?
- How to determine toxicity against normal cells in a situation closer to what a patient will face?

### Novel multiplex digital PCR assays were developed to monitor residual AML and CART in PDX mice





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### Competitive BM/AML xenografts were generated to test in vivo selectivity of UCART123







**Cell recruitment:** Endothelial, T<sub>reg</sub>, fibroblast



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Epithelial to mesenchymal transition (EMT)

2



**Cell recruitment:** Endothelial, T<sub>reg</sub>, fibroblast



**Cell recruitment:** Endothelial, T<sub>reg</sub>, fibroblast



**Cell recruitment:** Endothelial, T<sub>req</sub>, fibroblast



**Cell recruitment:** Endothelial, T<sub>reg</sub>, fibroblast





Cancer cell migration



### **Checkpoint inhibitors**



Drug	Target
Nivolumab	PD-1
Pembrolizumab	PD-1
Atezolizumab	PD-L1
Cemiplimab	PD-1
Ipilimumab	CTLA-4
Avelumab	PD-L1
Durvalumab	PD-L1

Curr. Oncol. 2022, 29, 3044–3060

#### Some tumors have an aberrant proteome





Nature. 2016 Oct 20;538(7625):397-401 Cancer Cell 36, 559–573, November 11, 2019

### Using epichaperome assessment for precision medicine



### Can the epichaperome detection assay be used to tailor therapies?



### Case: PM254

- A 61 year old woman diagnosed with an accelerated phase <u>myeloproliferative neoplasm</u> in 2013.
- Negative for BCRABL, PDGFRA/B and FGFR1 rearrangements as well as JAK2 mutation.
- Underwent <u>matched unrelated donor allogeneic stem cell transplantation</u> in 2014 for early recurrence.
- In Jan 2016, she **relapsed** and was treated with hydroxyurea.
- Atypical presentation of GVHD and treated successfully with ruxolitinib.
- In 2017, BM biopsy showed progression to AML with fibrosis.
- She developed progressive splenomegaly and weight loss and was treated with 2 cycles of decitabine without response.

## PM254 has a novel gene fusion (PML-SYK) and high epichaperome abundance



#### PU-H71 trial single patient IND results in CR



# **Recovery of normal blood forming colonies after treatment**



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#### **Precision Medicine**



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