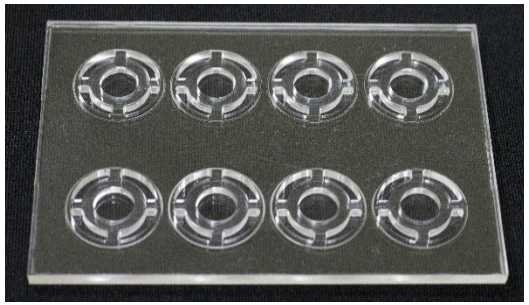
Microfluidic Organ-on-a-chip Models for Cancer Drug Screening And Safety Assessment In Vitro

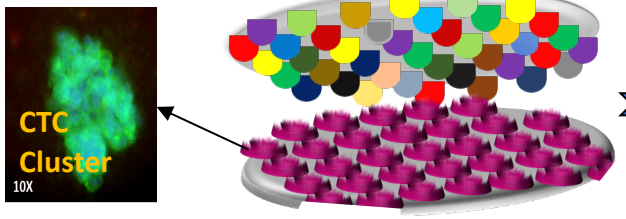
微流體器官晶片系統模型應用於癌症藥物篩檢與安全性評估

1. HD-SACA chip for CTCs/CTM/CHCs detection



2.AI-PRS drug screening

10 drugs x 5 conc. Cocktail chip



CTC clusters chip

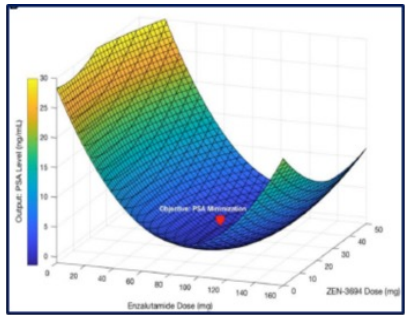
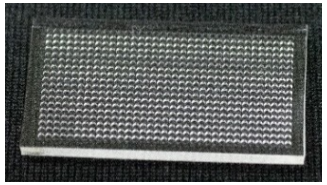
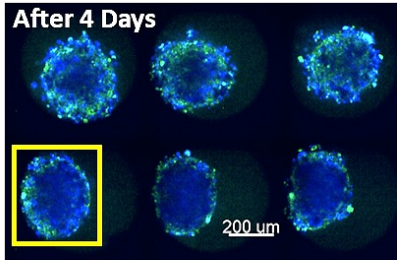
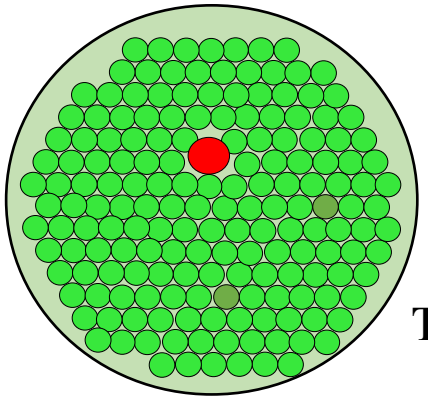


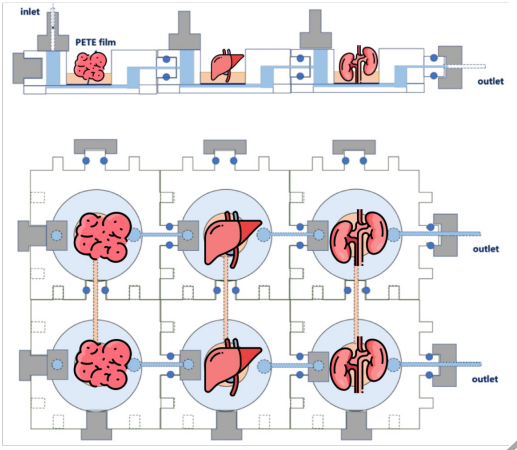
Figure 3: AI-PRS calibration of patient's AI-PRS profile with enzalutamide and ZEN-3694 doses and PSA levels. Using the patient's profile, the objective of minimizing the patient's PSA level is achievable by recommending the appropriate dose adjustments of enzalutamide and ZEN-3694 (red arrow).

3. 3D Tumor/Kidney/Liver on a Chip







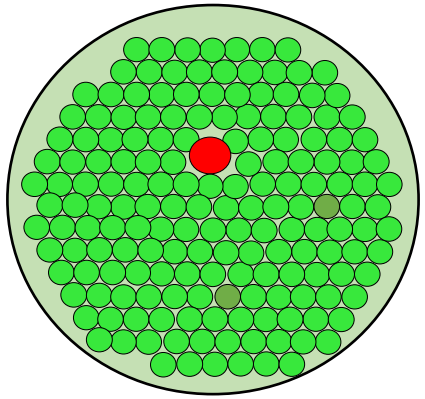


Prof. Fan-Gang Tseng (ASME Fellow)

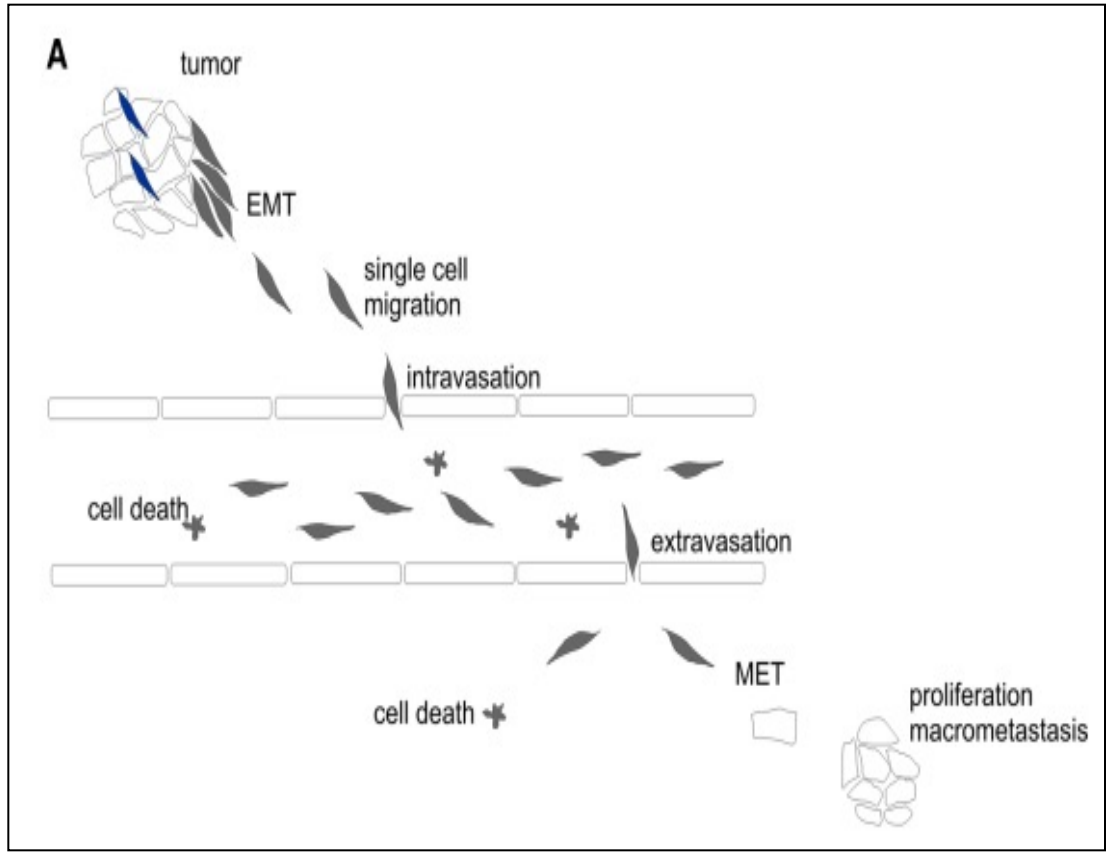
曾繁根 清華講座 教授

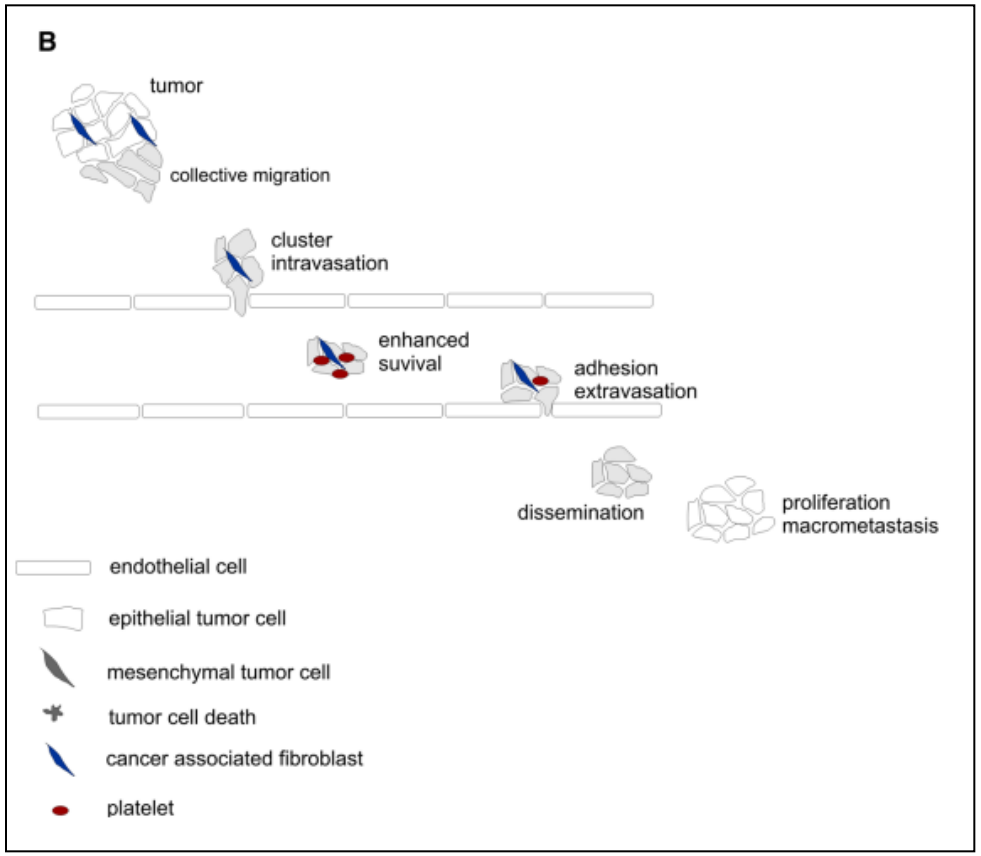
TsingHua Chair Professor, NTHU ESS/INEMS/Chemisrty, Taiwan
Affiliated Research Fellow, Academia Sinica, Taiwan

Part I: SACA systems enabled CTC/CTM identification for Cancer Diagnosis/Prognosis



Circulating tumor Cells (CTCs) and Circulating tumor microemboli (CTM)



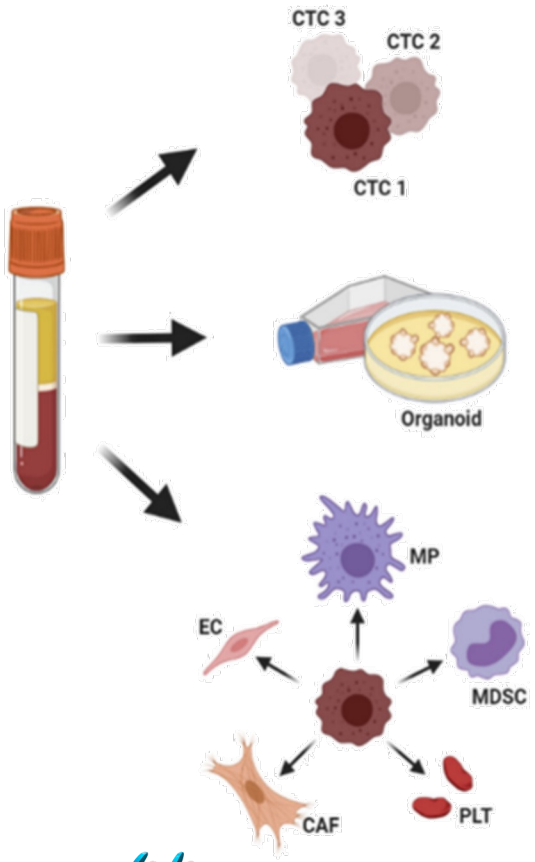


CTM have higher stemness, survival and metastatic growth possibility (30-50 times) than single CTCs.

(Image source: Fabisiewicz, Anna, and Ewa Grzybowska. "CTC clusters in cancer progression and metastasis." *Medical Oncology* 34.1 (2017): 12.

Circulating Tumor Cells from Enumeration to Analysis

There are now efforts to characterize CTCs more precisely through molecular and functional analysis, expanding the CTC effort from one of diagnosis and prognosis to now include the use of CTCs to specifically target cancers and discover therapeutic solutions, establishing CTCs as critical in precision medicine.



Single-cell analysis

- Assessment of intratumoral heterogeneity
- Elimination of leukocyte contamination

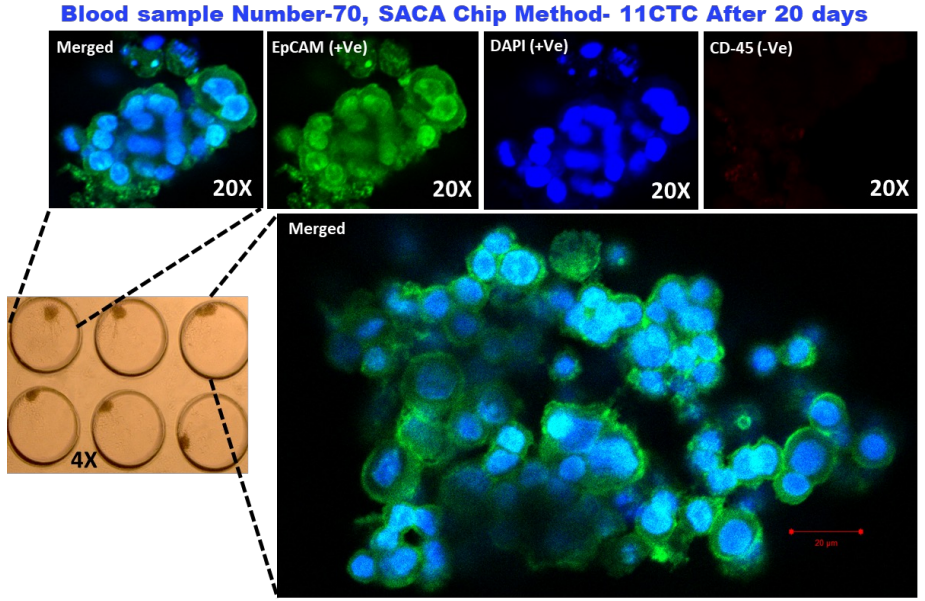
Ex vivo expansion

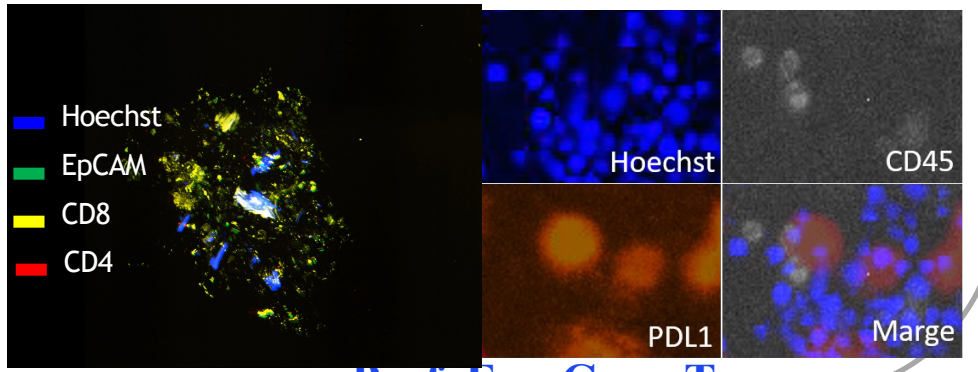
- Individualized testing of drug susceptibility
- Characterization of tumor's physiological and biological properties

CTC-associated cells

- Novel diagnostic and prognostic markers
- Novel therapeutic targets for combination therapies.

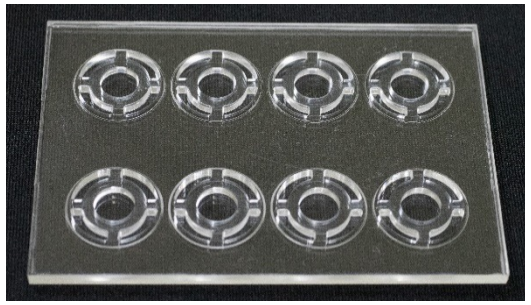
Yu-Ping Yang, Teresa M. Giret and Richard J. Cote, Cancers 2021, 13, 2723



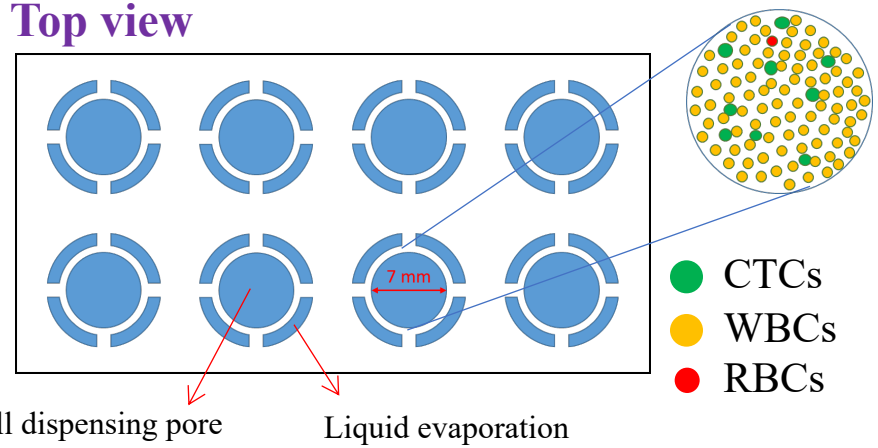


High-density Self-Assembly Cell Array (HD-SACA) Chip

Pure passive force (without pump)



Top view

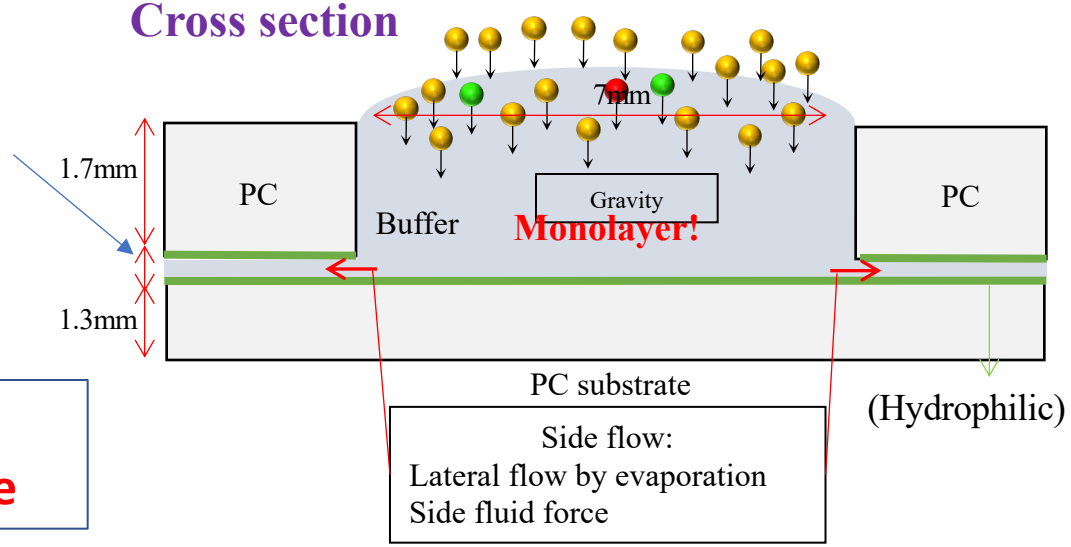


Cells > 10μm

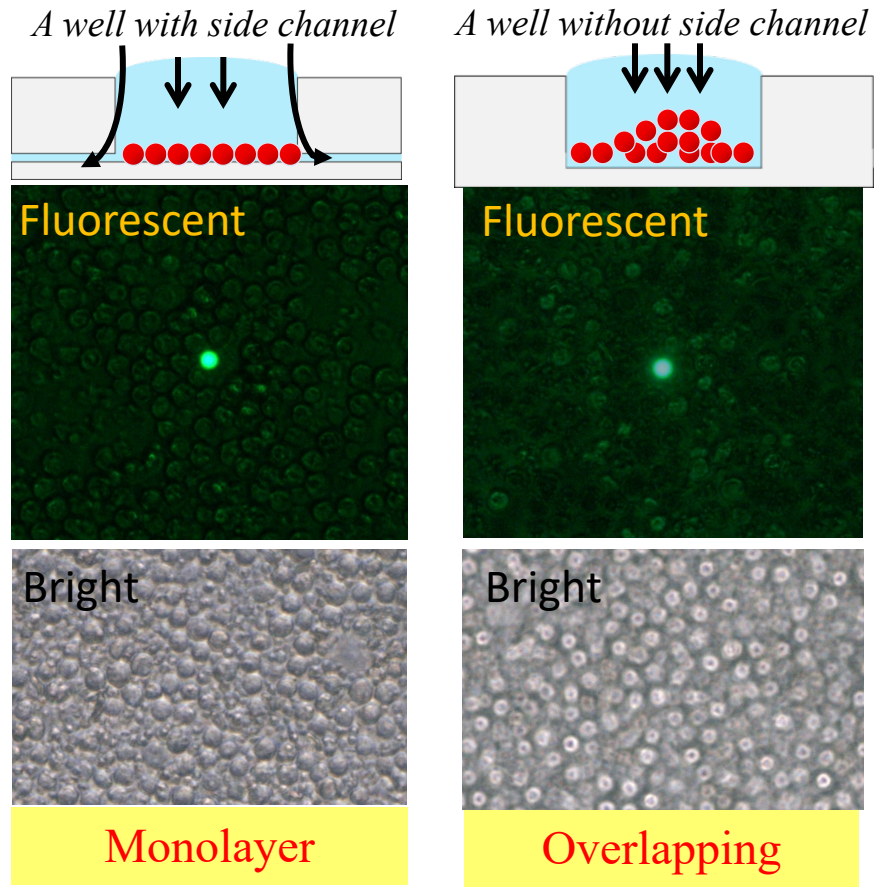
Cell restriction channel < 5μm

Cells trapped in observation hole

Cross section



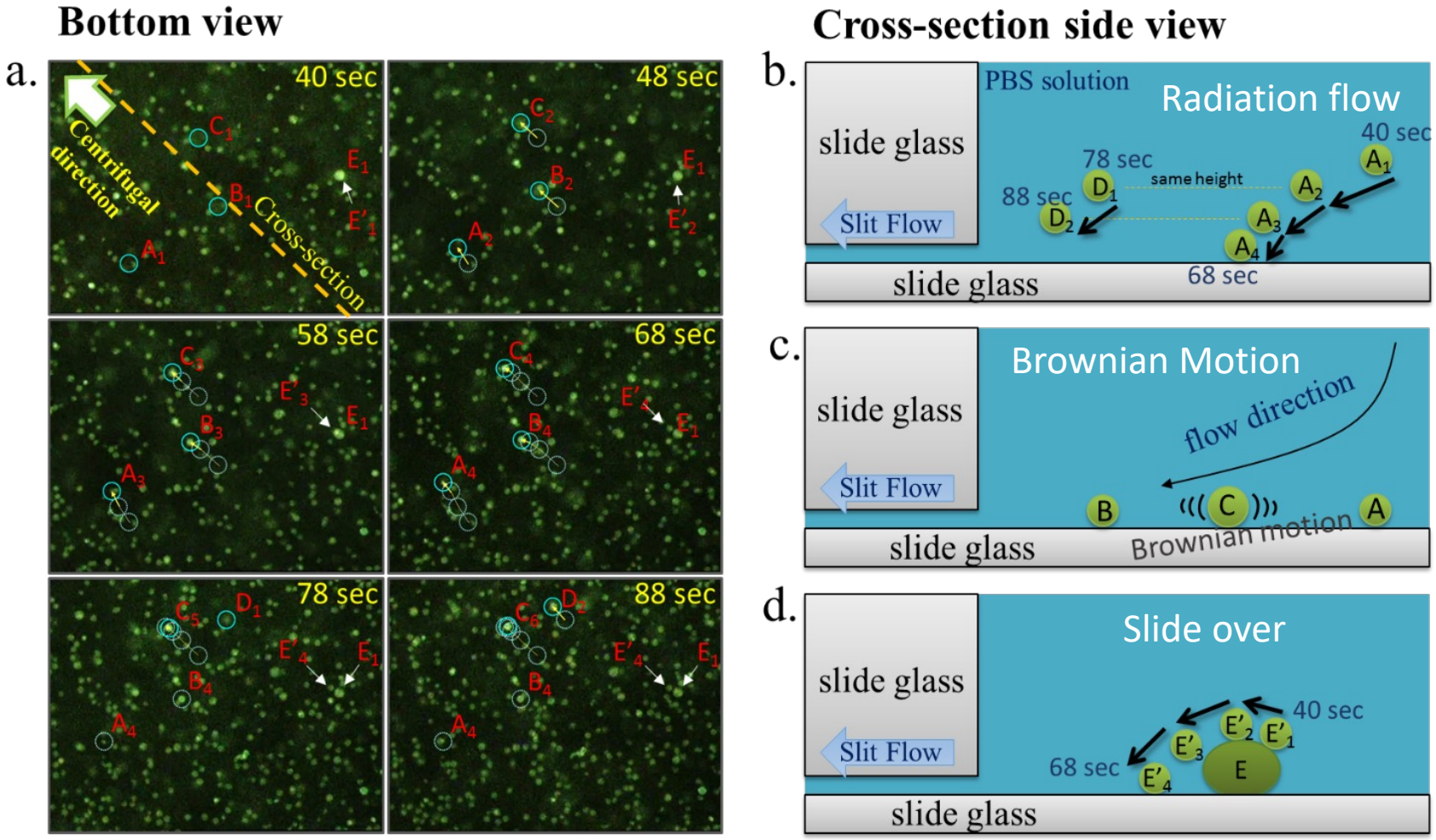
SACA chip avoid cell aggregation which interference observation



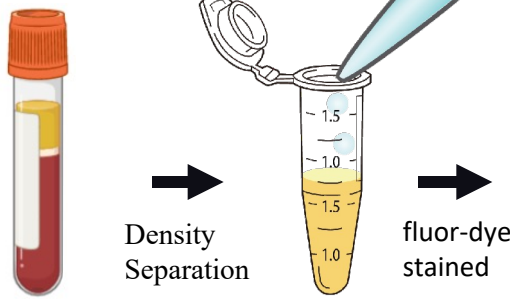
Easy to recognize and isolate

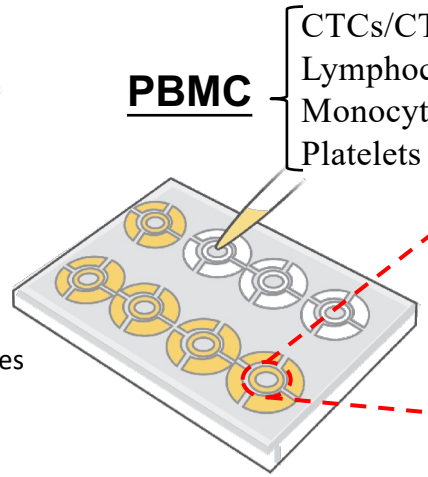
TJ Chen et. al. Biomicrofludics, 2014 ; WY Cho et.al., Sci. Rep. 2018

Mechanism for Cell Self-Assembly



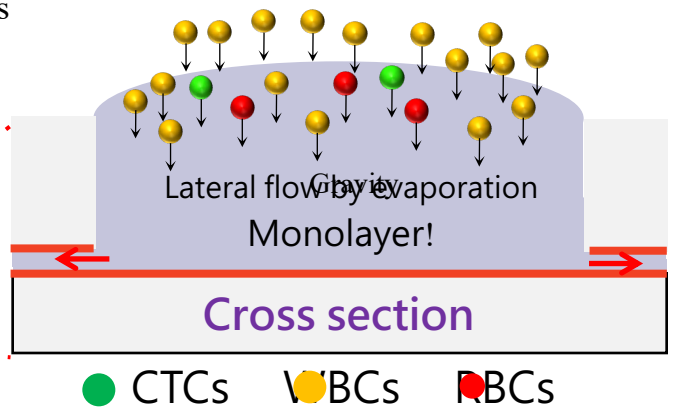
Workflow of CTCs/CTMs Detection





Step 1. Blood Sampling

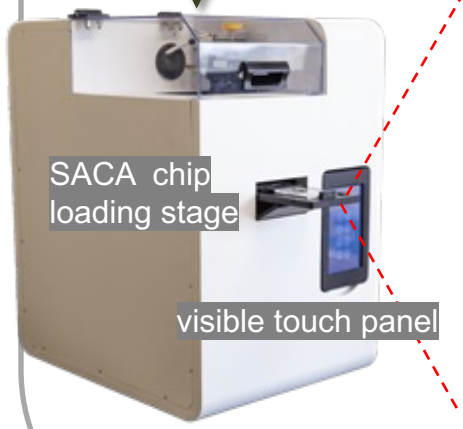
Step2. Cell IF staining

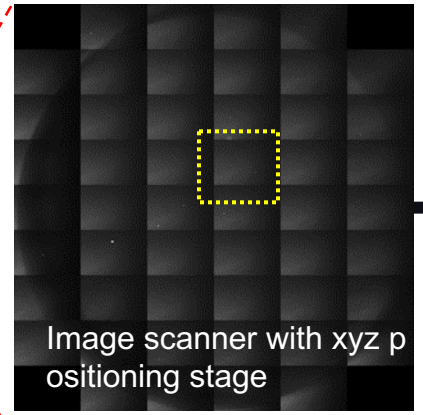


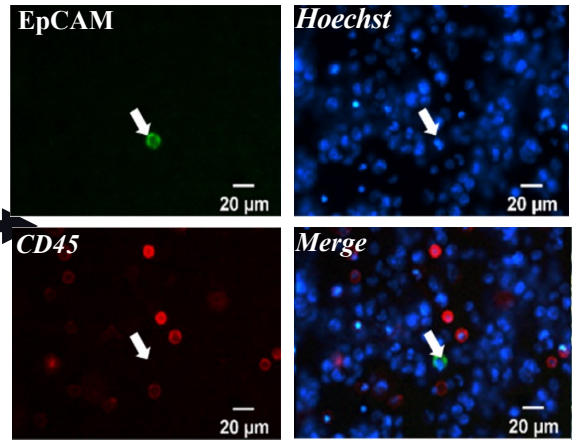
Step 3. fnRBC isolation from PBMC smear in a monolayer by SACA chip

Self Assembled Cells Array Chip

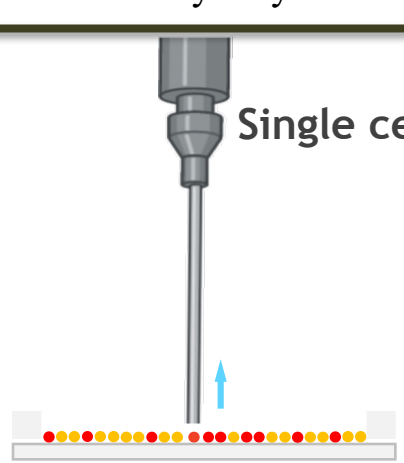


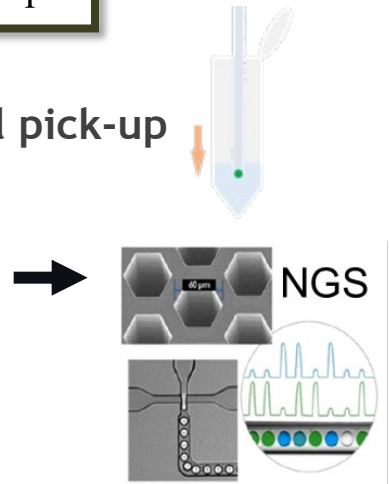






Step 4. Image screening and positing of fnRBC





Step 5. fnRBC counting and single cell sorting

Venkatesh et. al. Sen.Act. B, 2019, Venk. ACS AMI 2021

YJ Hao, Clinical Med. 2022

Rare Cell Screening and Single Cell Analysis System

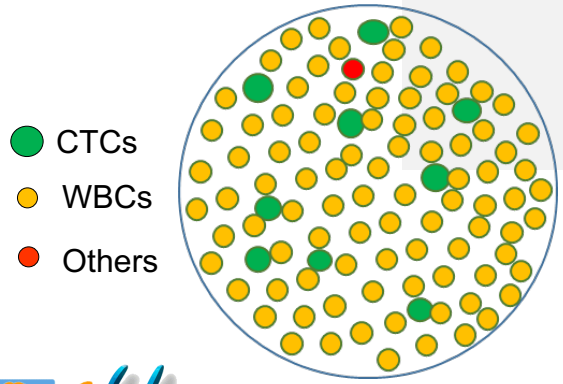
www.cellenvision.biz

† **The first demonstration case is a CTCs scanning chip system for monitoring disease progression and prediction of recurrence of Cancer.**

SACA Chip

www.cellenvision.biz

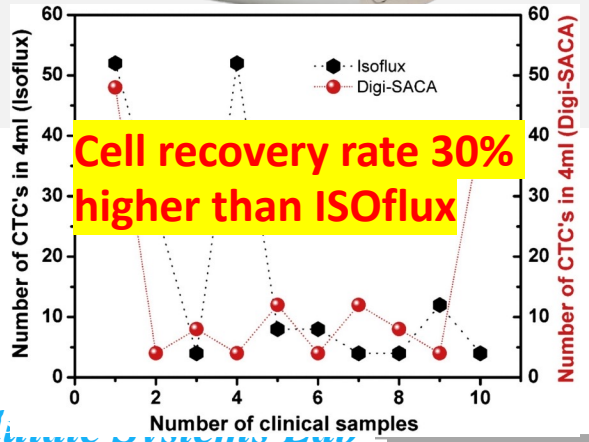




SACA Image System

CytoSCM imaging@cellenvision





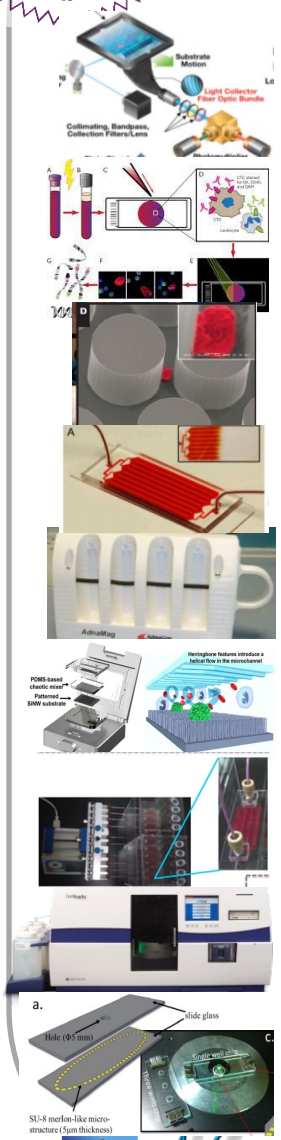
*System feature:

- Open chamber, Cell Monolayer
- Fluorescent imaging of CTCs
- Realtime Tracking
- Single cells/clusters pick-up

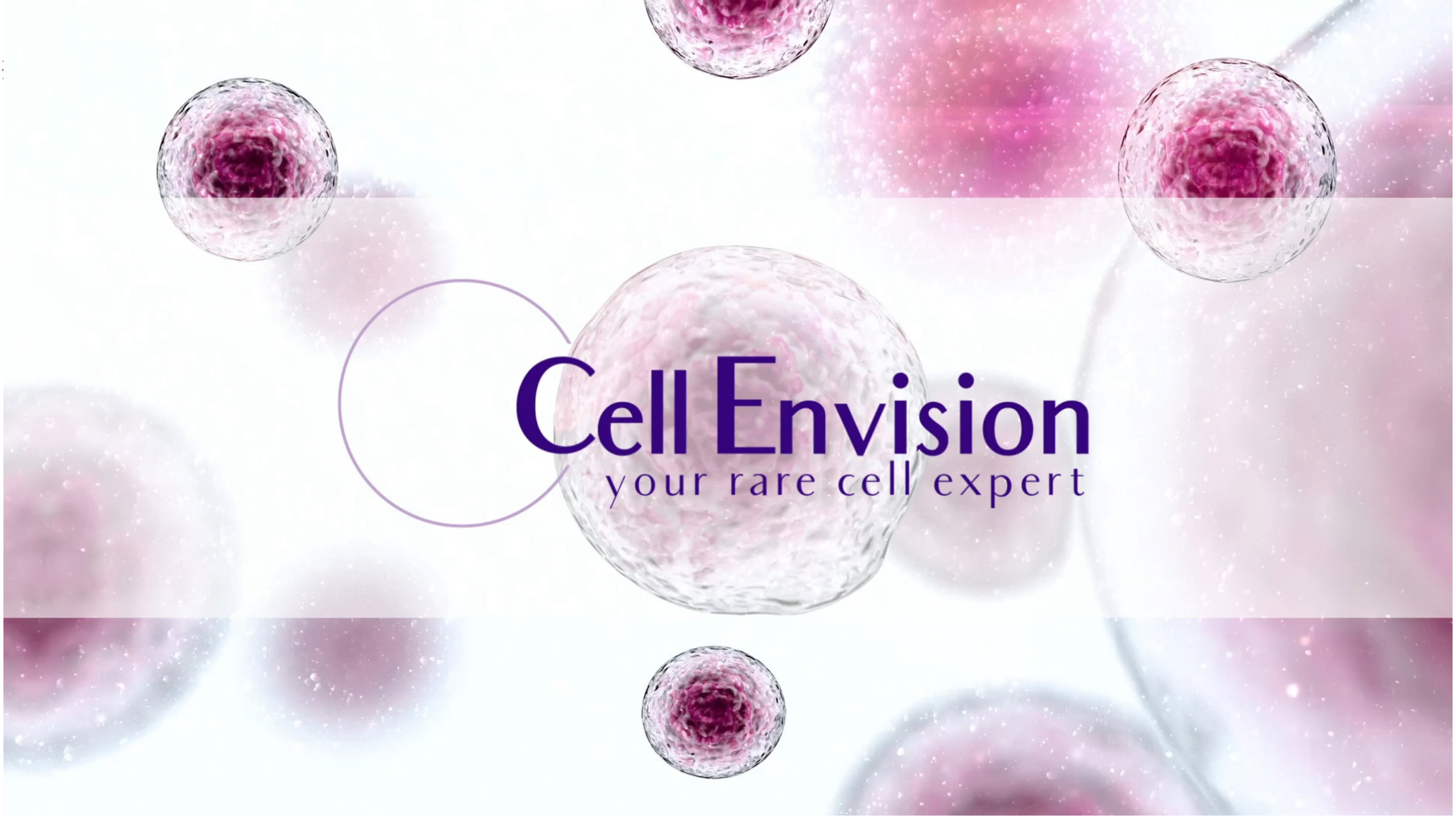
*Function capability:

- Resolution: **1/10^9**
- Recovery Rate: **> 95%**
- Cell assembly: **5 mins**
- Cell density: **10^6 cells/cm^2**
- Image time: **<1 hrs for 10^7 cells**
- Capture capability: **1 cell/0.1 cc**

Venkatesh et. al. Sen.Act. B, 2019



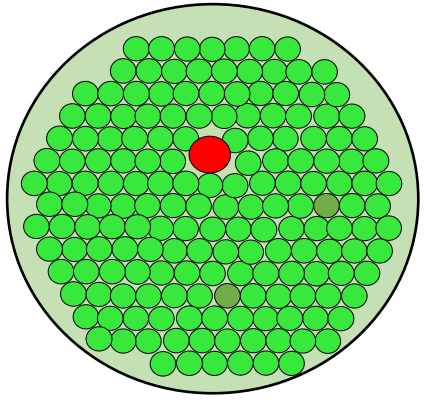
Name	Commercial /Technology	Automation	Recognition		Speed	Cost	Repeatability	Clinical trial	Cells viability	FDA
			Signal	Shape						
FAST	Partial fluorescence image	Low	✓	✓	80+80 min(In Lab)	EH	M	S	Dead	N
HD-CTC	Partial fluorescence image	Low	✓	✓	80+80 min(In Lab)	EH	H	L(3y)	Dead	N
CTC-Chip	Research immuno Fluorescence	No	✓		8~9 hr	M	L	S	Low	N
BD-Chip	Research immuno Fluorescence	No	✓		8~9 hr	M	L	S	Low	N
AdnaTestR (RT-PCR)	Commercial RT-PCR	No	✓		~4hr	H(RT-PCR)	H	m	Dead	N
CytoTrapNano™Chip	Commercial Immune Fluorescence	Half	✓	✓	X	X	EH	EL(ys)	Dead	N
CellMax-LBx CMxR	Commercial ctDNA	Half	✓		X	US $1000/CASE	EH	EL(ys)	Med	N
CellSearchRFluxion	Commercial Immune-magnetic	Half	✓	✓	8 Parallel 4hr	EH $1000/CASE	EH	E(ys)L	Dead	Y
NTHU-HD-SACA system	Research fluorescence image	Half	✓	✓	1-2 hr	US $100/CASE	EH(In Lab)	S(5ys)	High	N


Cell Envision
your rare cell expert

Part I: SACA systems enabled CTC/CTM/CHC/T cells/NK cells identification for Cancer Diagnosis/Prognosis

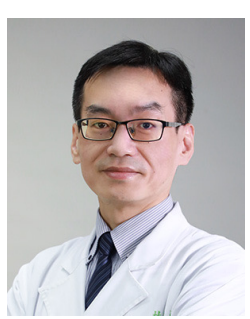
--More than 2000 clinical samples were completed since 2015.

(Clinical Medicine 2023, Advanced Therapeutics 2023, Sensors and Actuators B 2023, Cancers, 2020, 2019, Cells 2020, Sci. Rep. 2017, BMF 2014, MicroTAS 2011, 2012, 2013,2016, 2017, 2018, 2022, 2023, 2024, 2025, IEEE MEMS 2011)





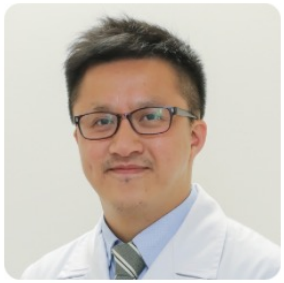
NVGH Dr. CK Chiang, Dr. CG Lin
CRC Cancer



SHH, Dr. KY Lee
Lung Cancer



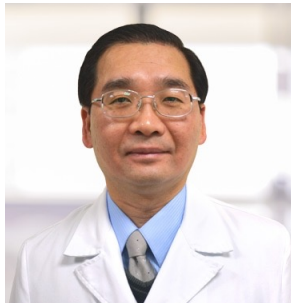
NTU H, Dr. ZS Lee
Lung Cancer



SKH, Dr. HC Lai
Breast Cancer



NTU H, Dr. S Wu
Head neck cancer
Pancreatic Cancer



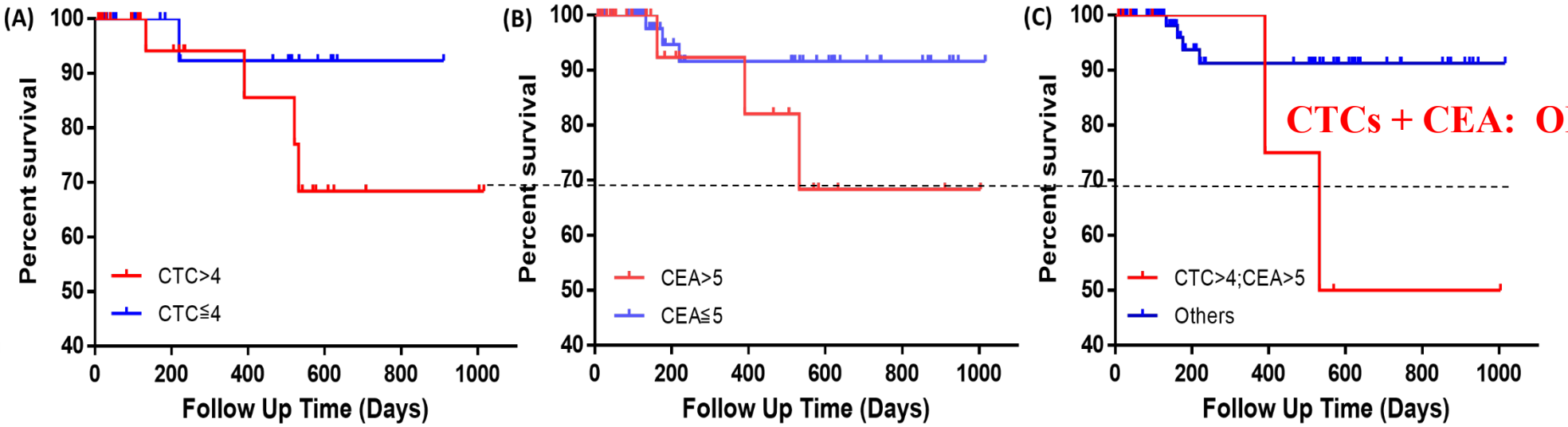
NTU H, Dr. CC Ke
Lung Cancer

CTCs Synergizes with CEA to Improve Prediction of Recurrence in non-metastatic CRC

Cancers 2019, 11(1), 56; Fangang et.



NVGH Dr. CK Chiang



CTCs + CEA: ORs>8.2

Figure X. Kaplan–Meier survival curves of progression-free survival in patients with non-metastatic diseases, stratified with CTC and CEA. (A) Red line: CTC >4; blue line: CTC ≤4; p = 0.242; (B) red line: CEA >5 ng/mL; blue line: CEA ≤5 ng/mL, p = 0.176; (C) red line: both CTC >4 and CEA >5 ng/mL; blue line: others, p = 0.033.

By long-term(>3 years) Number of CTC clusters tracking, it is possible to identify CTCs in the blood 1-1.5 years before the recurrence and metastasis of tumor, and improve postoperative survival rate with the odds Odds ratios (ORs) of CTCs with CEA >8 folds than CTC or CEA respectively.

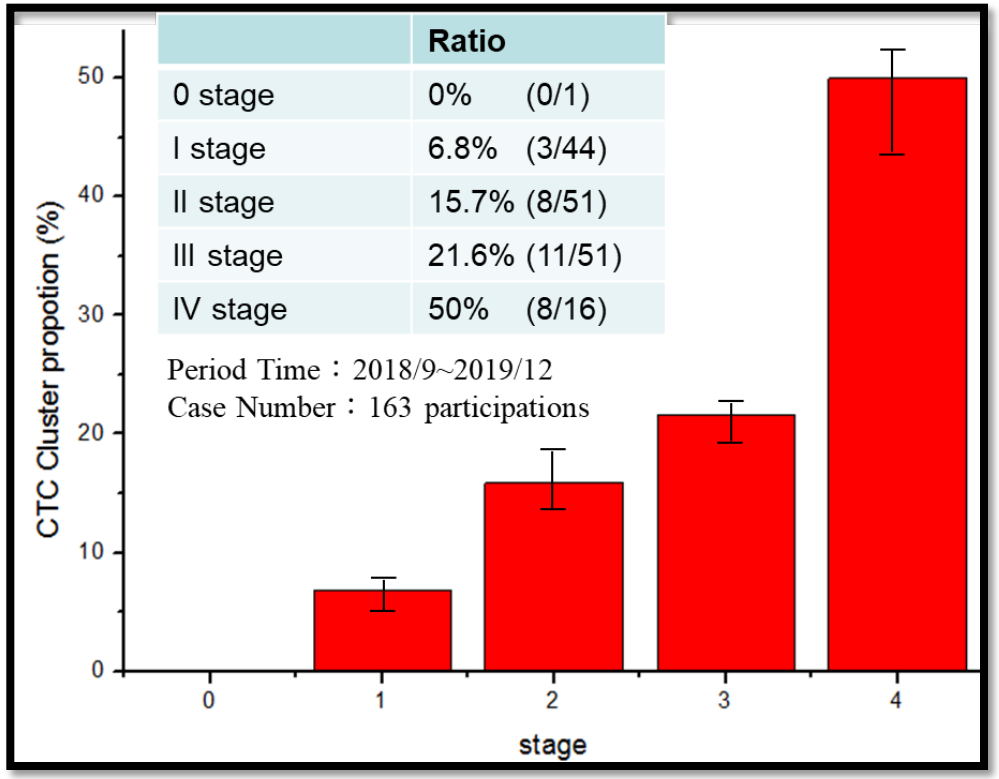
HY Chu et. al. Cancers, 2019

The CTM counts can best predict recurrence in patients with non-metastatic CRC

CTM numbers highly correlate with tumor stage

	Ratio
0 stage	0% (0/1)
I stage	6.8% (3/44)
II stage	15.7% (8/51)
III stage	21.6% (11/51)
IV stage	50% (8/16)

Period Time：2018/9~2019/12
Case Number：163 participations



"Highly Correlated Recurrence Prognosis in Patients with Metastatic Colorectal Cancer by Synergistic Consideration of Circulating Tumor Cells/Microemboli and Tumor Markers CEA/CA19-9" Cells, VOL.10, Issue 5, 1149, MAY, 2021

Odds ratios (ORs) of CTCs, CEA, CA19-9, and CTC clusters and their combination to predict recurrence for patients at all cancer stages

All Cancer Stages (163 Cases)	No. of Cases			
CTCs per 2 mL Blood	Recurrence	No Recurrence	Recurre	
CTCs > 3	16	34	3	
CTCs ≤ 3	7	106	6.	
CEA > 5	13	41	2	
CEA ≤ 5	10	99	9.	
CA19-9 > 37	8	14	36	
CA19-9 ≤ 37	15	126	10	
With CTC clusters	14	17	45	
Without CTC clusters	9	123	6.8%	
CTCs > 3; CEA > 5	10	12	45.5%	
Others	13	128	9.2%	8.2
CTCs > 3; CA19-9 > 37	4	3	57.1%	
Others	19	137	12.8%	9.6
CTCs > 3; With CTC clusters	11	6	64.7%	
Others	12	134	8.2%	20.5
CEA > 5; CA19-9 > 37	5	7	41.7%	
Others	18	133	11.9%	5.3
CEA > 5; With CTC clusters	7	8	46.7%	
Others	16	132	10.8%	7.2
CA19-9 > 37; With CTC clusters	5	4	55.6%	
Others	18	136	11.7%	9.4
CTCs > 3; CEA > 5; CA19-9 > 37	3	1	75%	
Others	20	139	12.8%	20.9
CTCs > 3; CEA > 5; With CTC clusters	6	2	75%	
Others	17	138	11%	24.4
CTCs > 3; CA19-9 > 37; With CTC clusters	1	1	50%	
Others	22	139	13.7%	6.3
CEA > 5; CA19-9 > 37; With CTC clusters	3	3	50%	
Others	20	137	12.7%	6.9
CTCs > 3; CEA > 5; CA19-9 > 37; With CTC clusters	3	0	100%	
Others	20	140	12.5%	N/A



NVGH Dr. CK Chiang

CTCs+CTMs+CEA: ORs>24.4

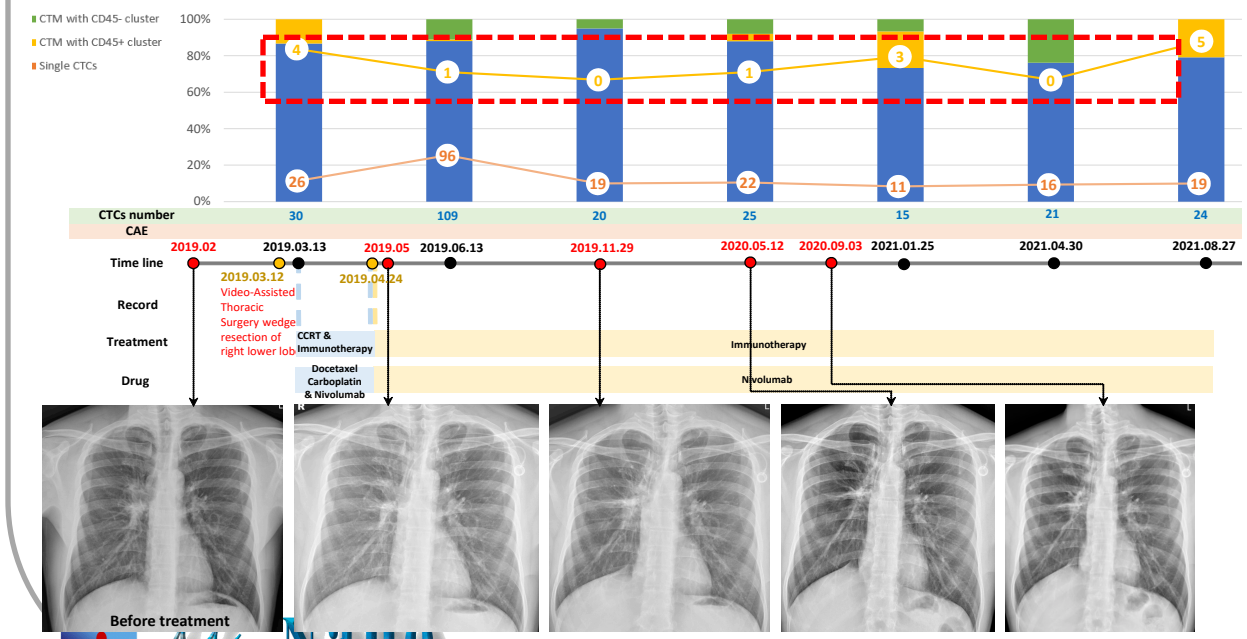
HY Chu et. al. Cells, 2020

POSTOPERATIVE FOLLOW-UP ON RECURRENCE DYNAMICS FOR NSCLC

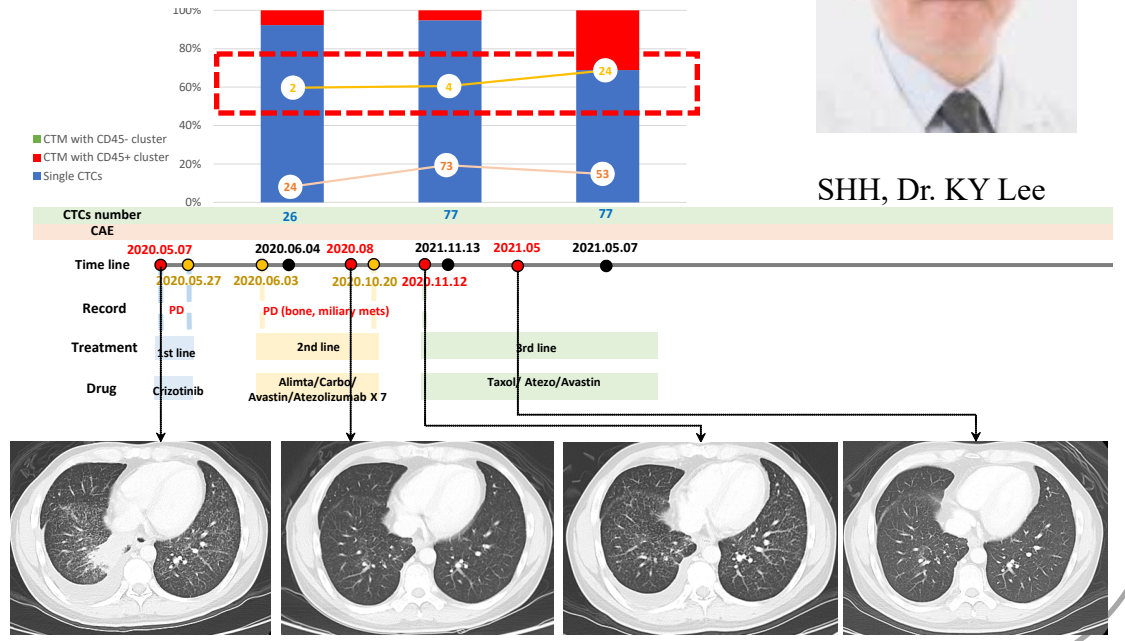
Lower CTM (CTCs cluster) activity illustrates more stable patient conditions

For lung squamous cell carcinoma stage IIIB, one has had tumors positive for PD-L1 expression as well as treated with Docetaxel + Carboplatin + Nivolumab), and the other has had tumors negitive for PD-L1 expression as well as treated with Alimta/Carbo/Avastin/Atezolizumab)

Positive case(CTM number & (CTC+CD45-) decreasing)



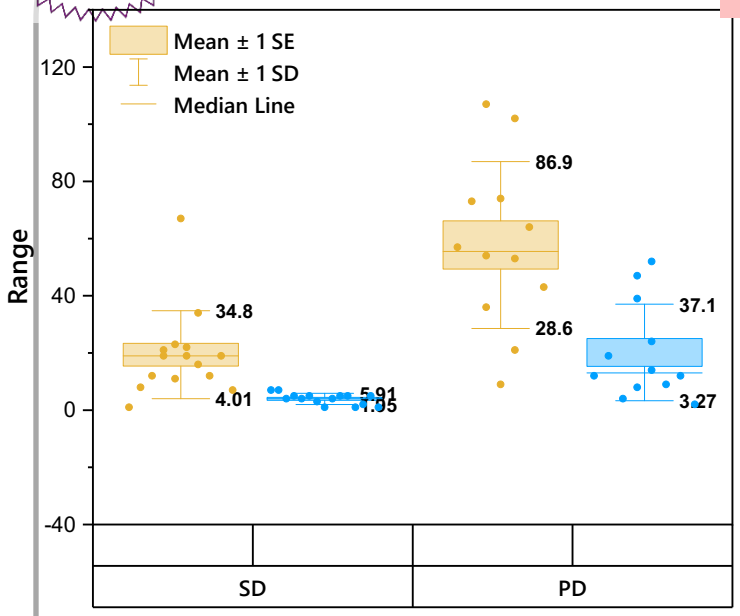
Negative case (CTM number & (CTC+CD45+) increasing)

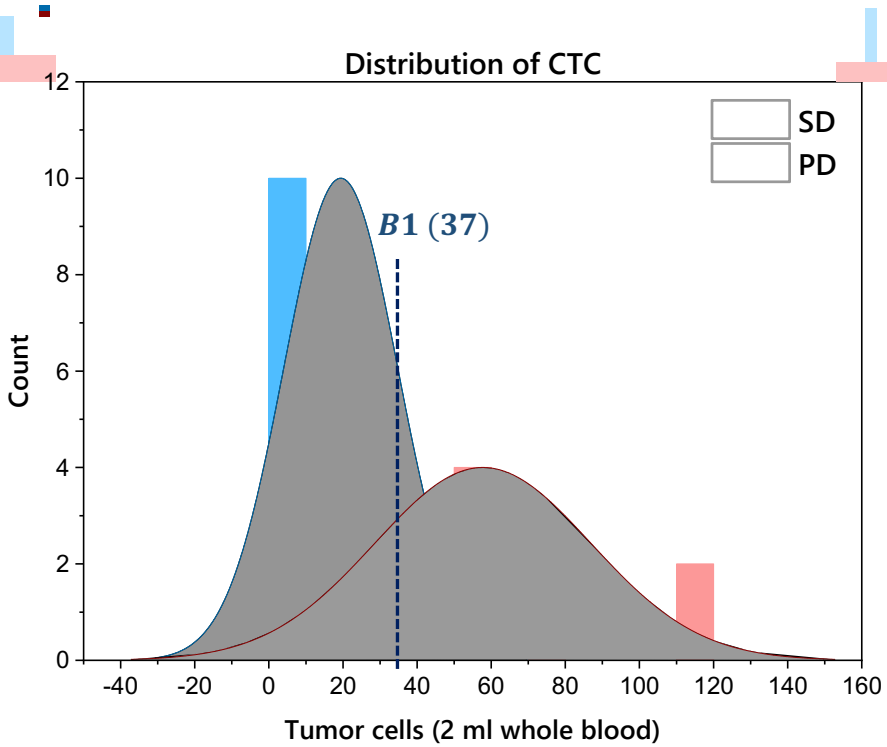


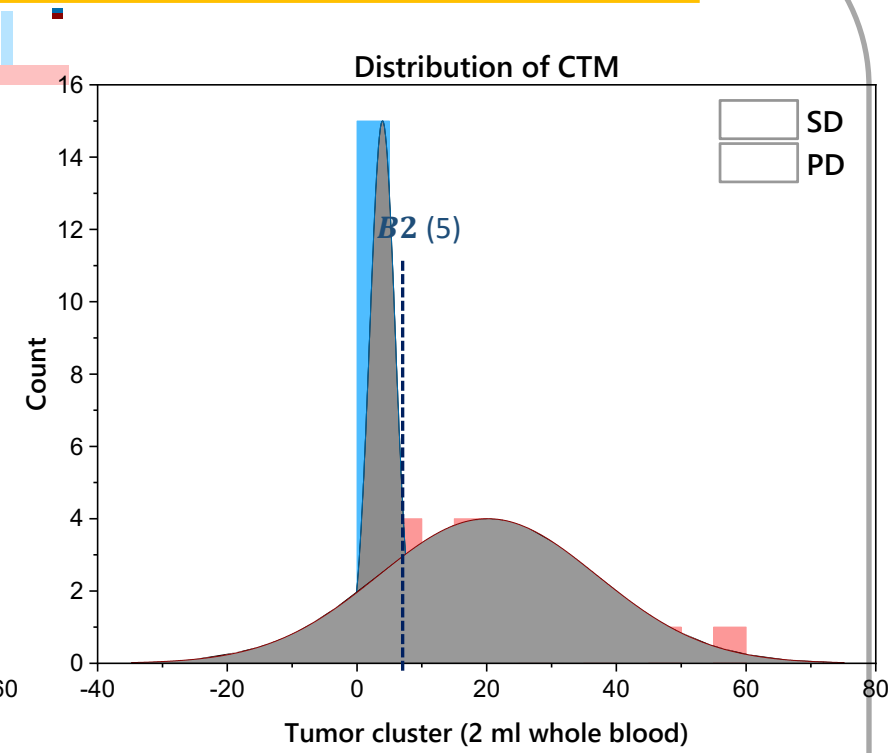


SHH, Dr. KY Lee

Distribution of CTC and CTM numbers to PD and SD cases







CTC*: *Patient's state point of CTC

CTM*: *Patient's state point of CTM

A1*: *Predict accurancy of CTC

A2*: *Predict accurancy of CTM

B1*: *cut − off point of CTC

B2*: *cut − off point of CTM

$$CTC\ Factor = A1 \times \frac{CTC - B1}{B1}$$

$$CTM\ Factor = A2 \times \frac{CTM - B2}{B2}$$

Combine

$$\text{P Score} = A1 \times \frac{CTC - B1}{B1} + A2 \times \frac{CTM - B2}{B2}$$

P score (Combined Predition Scores of CTC/CTM) for PD Risk Assessment

CTC	CTM	C Score	state
19	1	-0.60649	0
22	3	-0.29446	0
11	4	-0.45523	0
16	5	-0.21051	0
19	5	-0.13449	0
12	4	-0.42989	0
74	14	2.321371	1
21	8	0.2702	1
9	9	0.084086	1
73	4	1.116029	1
53	24	2.969171	1
54	52	6.298514	1
12	5	-0.31189	0
19	5	-0.13449	0
36	12	1.122343	1
64	19	2.657943	1
67	1	0.609971	0
43	2	0.119743	1
8	4	-0.53126	0
102	47	6.924971	1
23	2	-0.38711	0
226	144	21.51349	1
57	39	4.840543	1
107	12	2.921686	1
34	7	0.481657	0
21	5	-0.0838	0
7	7	-0.2026	0
1	1	-1.06266	0

0: SD
1: PD

$$\text{P Score} = 0.887 \times \frac{CTC-35}{35} + 0.885 \times \frac{CTM-7.5}{7.5} + 0.566$$

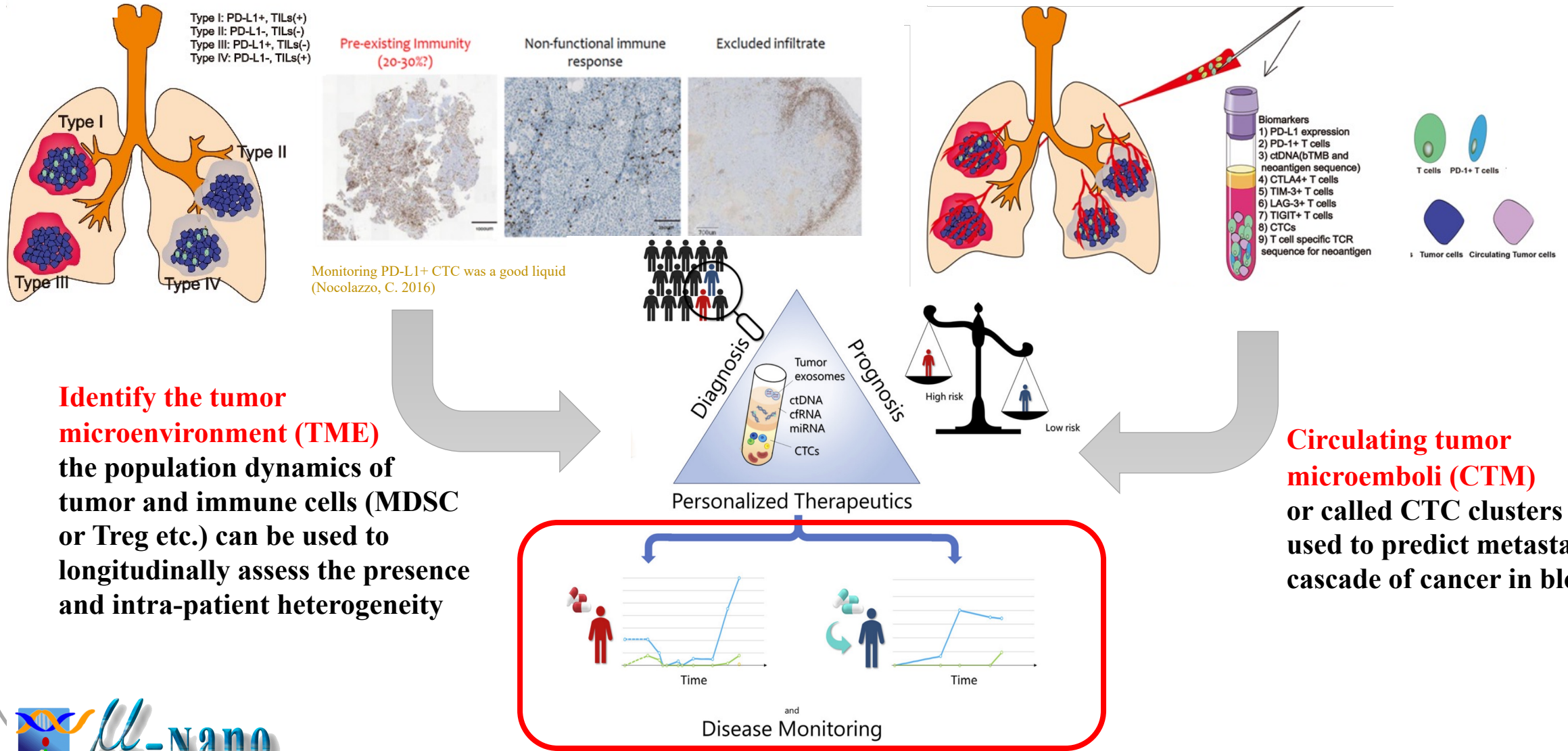
	CTC	CTM	PScore
Sensitivity	0.846	0.846	1.000
Specificity	0.938	0.938	0.812
AUC	0.887	0.885	0.957

Risk classification

Range	Total	PD	Recurrence rate
<0	13	0	0%
0~1	5	3	60%
>1	10	10	100%

- If only CTC or CTM is used for judgment, 6 status points of the appointment will be misjudged, and 5 points will be corrected after the combined judgment

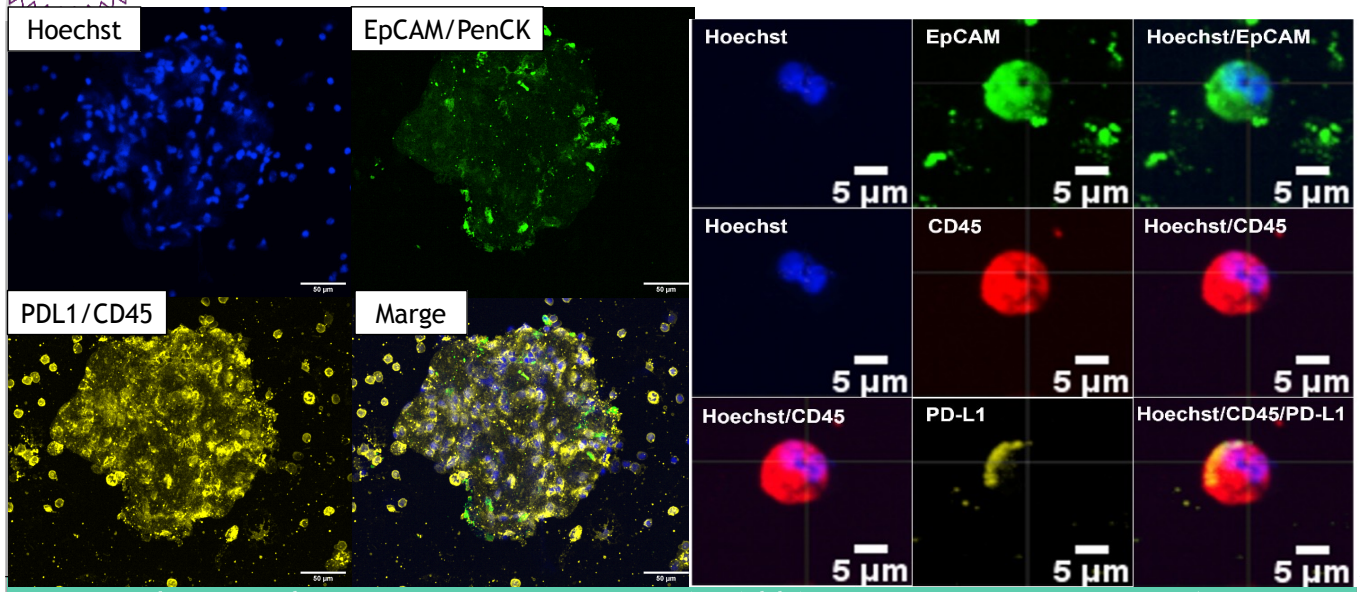
SOLID AND LIQUID BIOPSY FOR PDL1 DETECTION



Identify the tumor microenvironment (TME)
the population dynamics of tumor and immune cells (MDSC or Treg etc.) can be used to longitudinally assess the presence and intra-patient heterogeneity

Circulating tumor microemboli (CTM)
or called CTC clusters be used to predict metastatic cascade of cancer in blood

Correlation Between PD-L1 Expression and Outcome



Case study	Liquid biopsy			Tissue
(Dako,22C3)	Epcam	PDL1	CD45	PDL1
PBMC volume (2mL)		$2x10^6$		
CTC number	13	7		—
WBC number		42	126	
TPS SCORE		7/13 (TPS 54%)		0/100 (TPS 0%)
CPS SCORE		49/139 (CPS=35)		

Heavy smoker lung adenocarcinoma, stage IV with multiple metastases EGFR wild type, ALK (-), ROS-1(-), no driver mutation detected by ACT-Onco+ NGS panel, MSS, high tumor mutation burden (22 mutations/Mb), PDL1 0% by 22C3 assay, confirmed by 2 independent lab (NTUH and MSD central review).

GUIDE TO SCORING PD-L1 EXPRESSION USING COMB (CPS), 2021 Feb, MERCK



NTU H. Dr. ZS Lee

CPS ≥1 in the KEYNOTE-048 study

85% (n=754/882) of treatmen had tumors that expres

Cisplatin-ineligible patients with locally advanced or mUC

CPS ≥10 in the KEYNOTE-052 study

~30% (n=110/370) of patients with locally advanced or mUC who were not eligible for cisplatin-containing chemotherapy had tumors that expressed CPS ≥10.

Advanced gastric or GEJ cancer

CPS ≥1 in the KEYNOTE-059 study

(n=143/259) of patients with advanced gastric or

Our CTM-PD-L1 Expression (CPS score) as Biomarker for Therapeutic Efficacy of Immune Checkpoint Inhibition in NSCLC, and may to be met the guide to scoring PDL1 expression posted by Merck & Co., Inc.

CPS ≥10 in the KEYNOTE-181 study

27% (n=167/628) of patients in KEYNOTE-181 had ESCC and expressed PD-L1 CPS ≥10.

CPS ≥10 in the KEYNOTE-180 study

29% (n=35/121) of patients in KEYNOTE-180 had ESCC and expressed PD-L1 CPS ≥10.

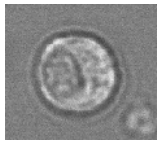
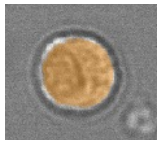
Advanced cervical cancer

CPS ≥1 in Cohort E of the KEYNOTE-158 study

79% (n=77/98) of patients with advanced cervical cancer had PD-L1 expression and received at least 1 prior line of chemotherapy in the metastatic setting.

Artifitial Inteligience differentiated Hperspectra for Single CTC analysis from patient blood sample

Spectral analysis - Compare Spectral line

Selected region diagram

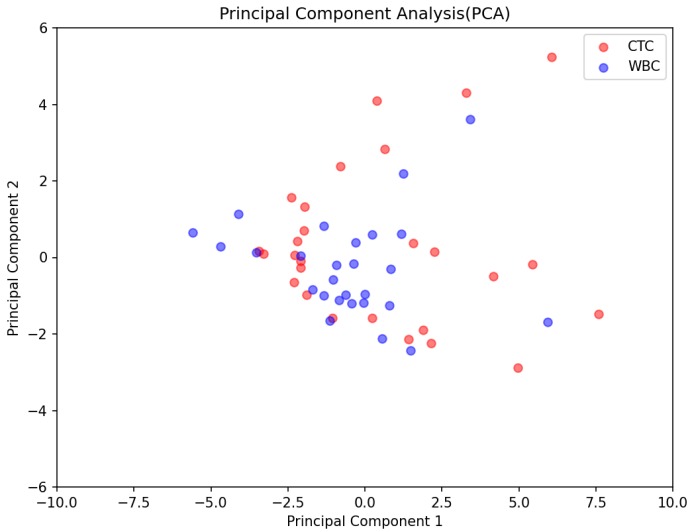
$$Z = \frac{x - \mu}{\sigma}$$

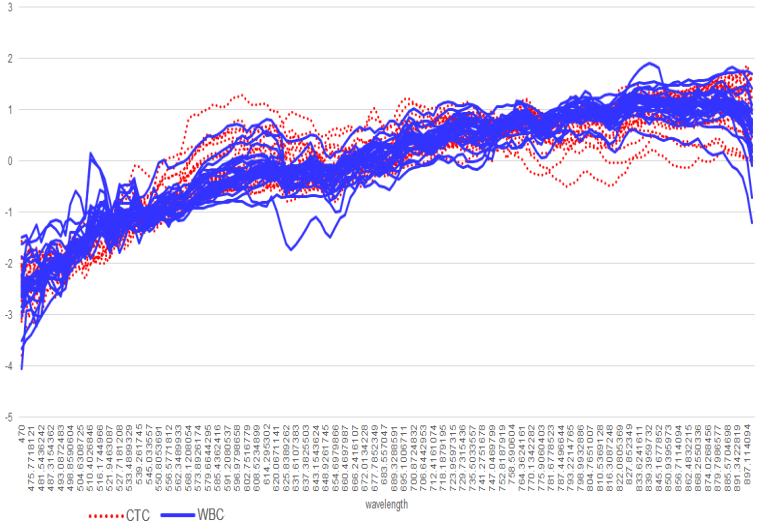
x: original value

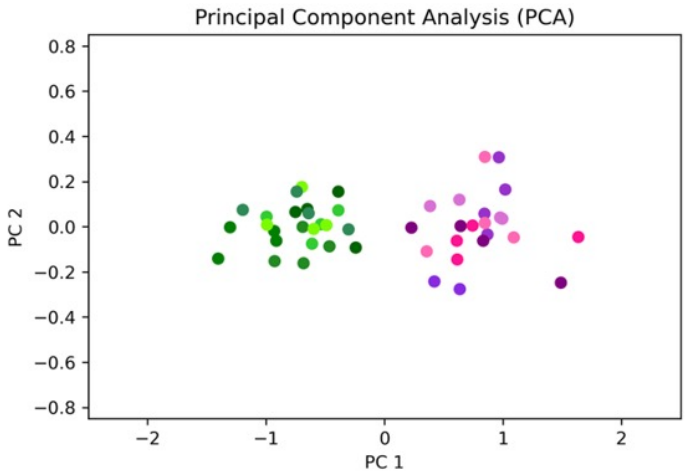
μ: mean of the hyperspectral image

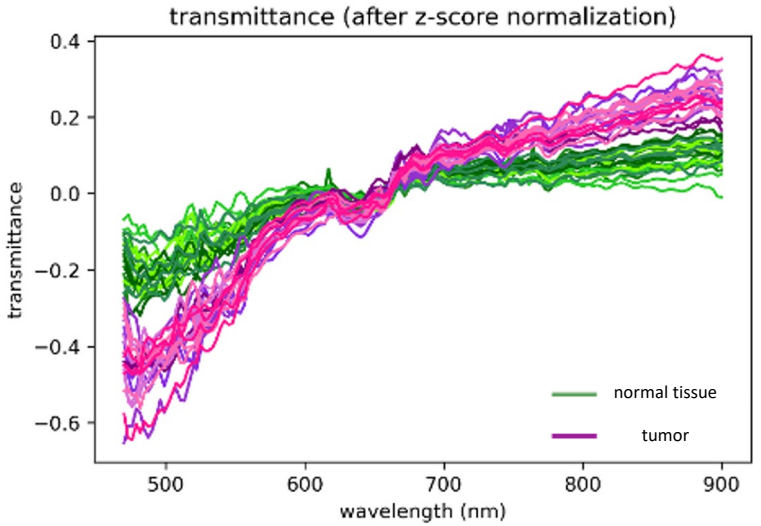
σ: standard deviation of the hyperspectral image

- Hard to distinguish from spectral lines
- After PCA still not significant



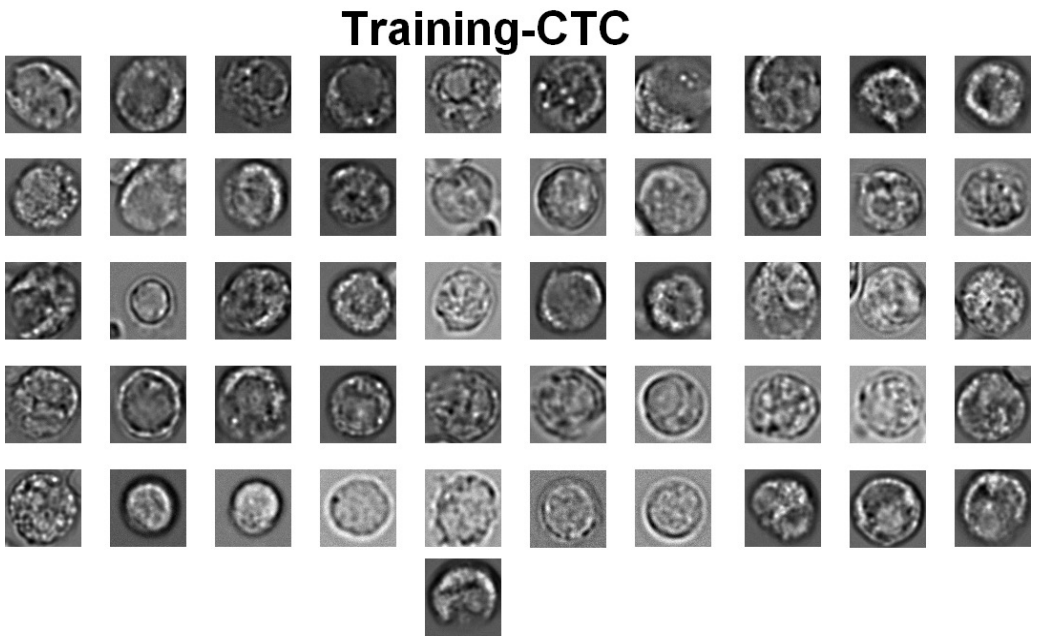




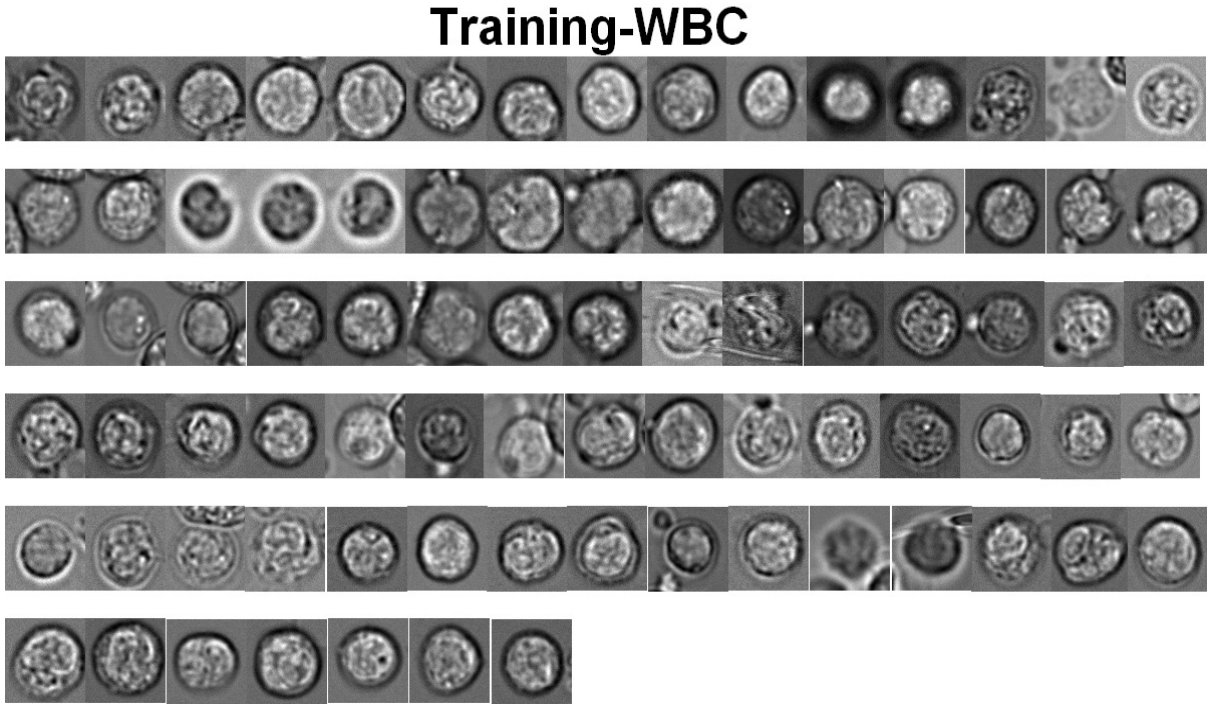


Structural analysis – ResNet50 (training set)

51 CTCs



82 WBCs



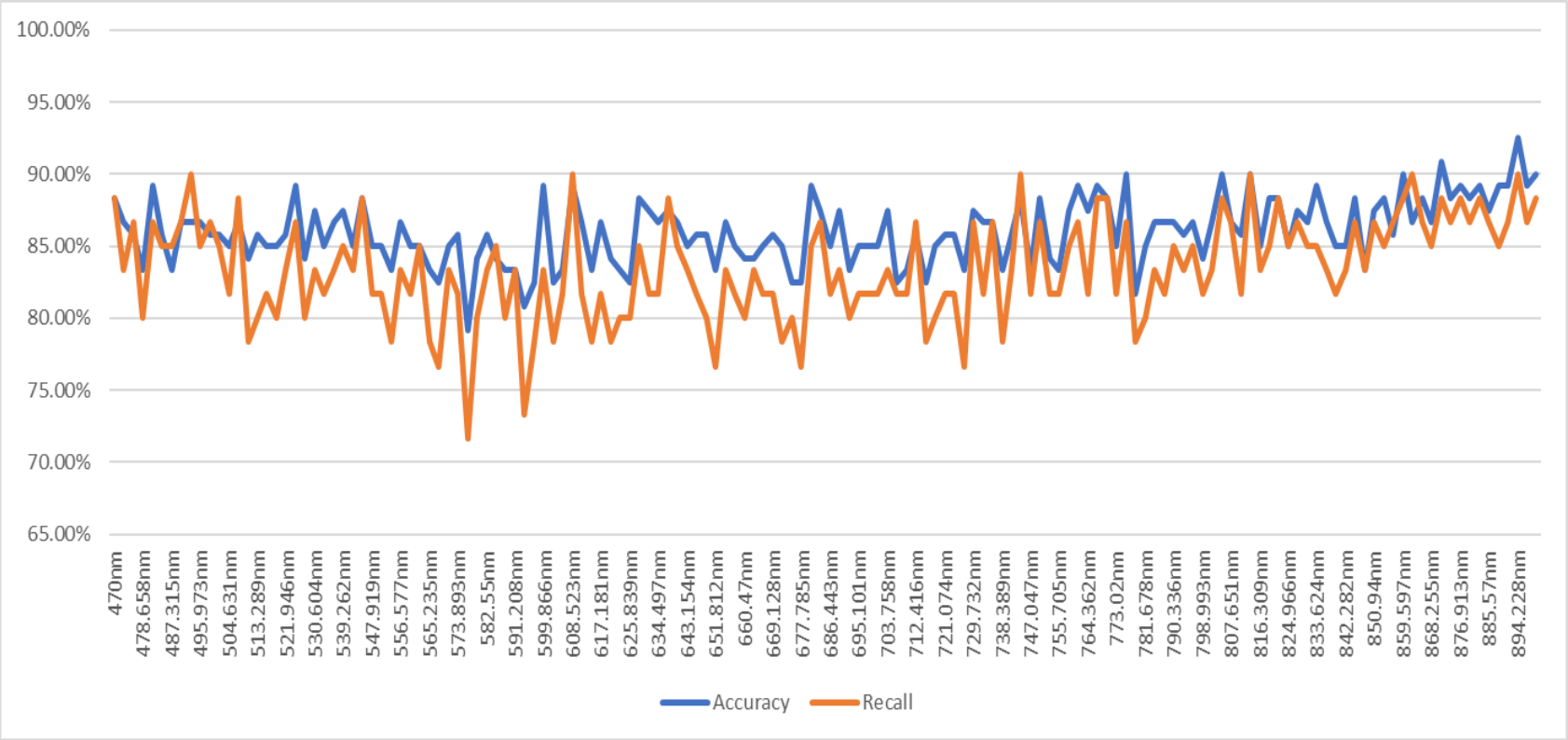
Structural analysis – ResNet50 (do cross-validation)



- Overall, a good recognition rate can be achieved
- Investigate whether the size of the data affects the results

Test	Accuracy	Recall	Precision
1	87.5%	87.86%	87.06%
2	66.67%	65.71%	65.71%
3	87.5%	86.43%	87.78%
4	95.83%	96.67%	95%
5	91.67%	91.11%	91.11%
6	100%	100%	100%
Average	88.195%	87.963%	87.777%

Structural analysis – Compare different wavelengths



470nm-900nm(150 bands)

Training Datasets:

CTC:80

WBC:160

Test Datasets:

CTC:20

WBC:20

Structural analysis – Compare different wavelengths

Accuracy

	wavelength(nm)							
	775.9	804.7	813.4	859.5	871.1	894.2	900	Mixed
Test1	92.42%	89.39%	87.88%	89.39%	92.42%	96.97%	95.45%	95.45%
Test2	89.39%	90.91%	93.94%	93.94%	98.48%	98.48%	90.91%	96.97%
Test3	93.94%	93.94%	95.45%	90.91%	95.45%	92.42%	92.42%	95.45%
Test4	90.77%	95.38%	90.77%	92.31%	96.92%	93.85%	95.38%	93.85%
Test5	89.23%	89.23%	89.23%	87.69%	87.69%	87.69%	86.15%	87.69%
Test6	92.31%	90.77%	90.77%	90.77%	90.77%	89.23%	93.85%	92.31%
Overall	91.34%	91.60%	91.34%	90.84%	93.62%	93.11%	92.36%	93.62%

Recall

	wavelength(nm)							
	775.9	804.7	813.4	859.5	871.1	894.2	900	Mixed
Test1	85.19%	92.59%	77.78%	85.19%	88.89%	92.59%	88.89%	92.59%
Test2	96.30%	92.59%	92.59%	88.89%	96.30%	96.30%	88.89%	96.30%
Test3	88.89%	88.89%	92.59%	81.48%	92.59%	85.19%	92.59%	92.59%
Test4	84.62%	92.31%	80.77%	84.62%	92.31%	84.62%	96.15%	88.46%
Test5	76.92%	84.62%	84.62%	80.77%	76.92%	73.08%	73.08%	76.92%
Test6	88.46%	80.77%	88.46%	88.46%	80.77%	84.62%	88.46%	84.62%
Overall	86.79%	88.68%	86.16%	84.91%	88.05%	86.16%	88.05%	88.68%

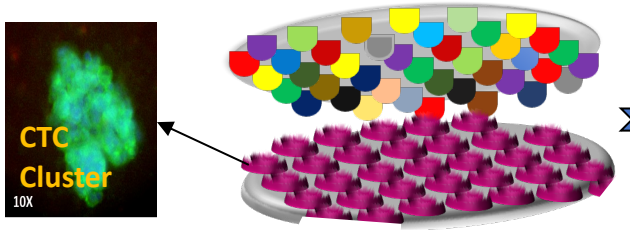
	Training	Testing
Test1	CTC:132 WBC:195	CTC:27 WBC:39
Test2	CTC:132 WBC:195	CTC:27 WBC:39
Test3	CTC:132 WBC:195	CTC:27 WBC:39
Test4	CTC:133 WBC:195	CTC:26 WBC:39
Test5	CTC:133 WBC:195	CTC:26 WBC:39
Test6	CTC:133 WBC:195	CTC:26 WBC:39

- Select the top seven wavelengths that performed best
- We can find that the mixing performance is relatively stable
- Mixing can achieve higher accuracy and recall

Part II: AI-PRS enabled precision medicine

AI-PRS drug screening

10 drugs x 5 conc. Cocktail chip



CTC clusters chip

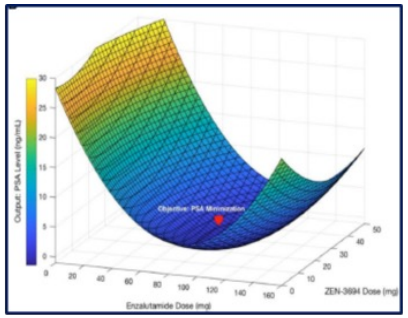


Figure 3: AI-PRS calibration of patient's AI-PRS profile with enzalutamide and ZEN-3694 doses and PSA levels. Using the patient's profile, the objective of minimizing the patient's PSA level is achievable by recommending the appropriate dose adjustments of enzalutamide and ZEN-3694 (red arrow).

AI-PRS Based Cocktail-Drug Treatment Process



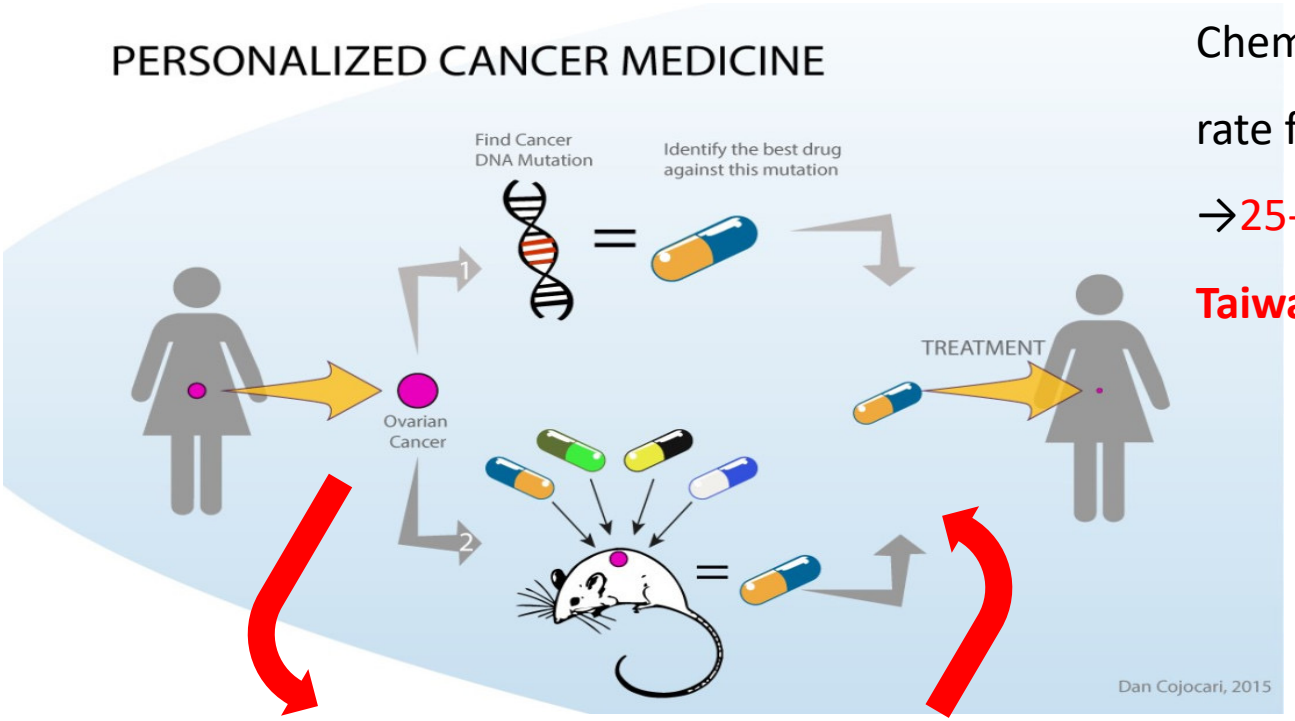
清華 曾繁根教授



UCLA 何志明院士



北醫 閻雲 校長

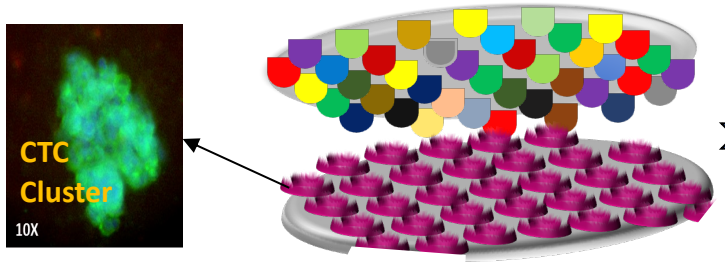


Chemotherapy response rate for CRC patients

→25-35% in US ; **15% in Taiwan!**

AI-PRS drug screening

10 drugs x 5 conc. Cocktail chip



CTC clusters chip

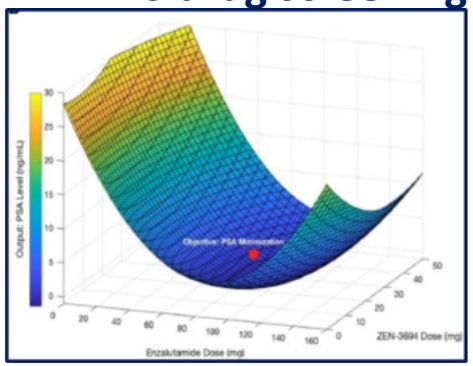
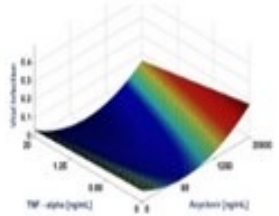


Figure 3: AI-PRS calibration of patient's AI-PRS profile with enzalutamide and ZEN-3694 doses and PSA levels. Using the patient's profile, the objective of minimizing the patient's PSA level is achievable by recommending the appropriate dose adjustments of enzalutamide and ZEN-3694 (red arrow).

Literature Review-

Artificial Intelligence Phenotypic Response Surface (AI-PRS)

Drug-Dose  $E(C, t) = x_0 + \sum_{i=1}^{N} x_i c_i + \sum_{i=1}^{N} y_{ii} c_i^2 + \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} z_{ij} c_i c_j$ Efficacy

linear drug effects on tumor response

quadratic drug effects

drug–drug interaction effects (synergistic or antagonistic)

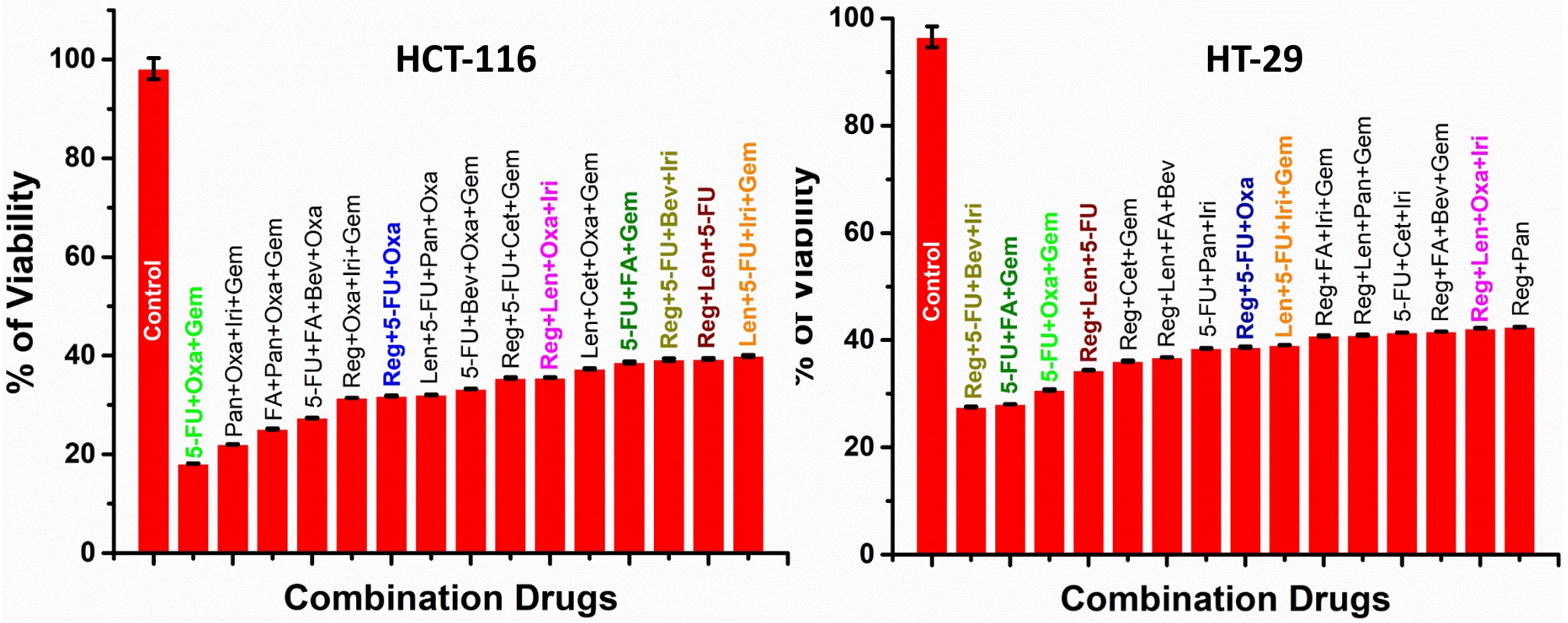
M drug	Calibration tests	Search space N^M (N=5)
4	15	625
10	**66**	**~10^6**
20	231	~10^{13}

PRS dictates the composition and the ratio of a globally optimized drug combination from a very large search space in *in vitro* tests.

C. M. Ho. et. al., *Science translational Medicine*, 2018.

AI-PRS based combinatorial drug screening (*in vitro*) for personalized medicine

5. Experimental results



- Top **15** ranked **3**, and 4 drug combinations out of **155** combinations.
- **The drug combinations highlighted with deferent color combinations are the universal combinations (7 combinations) for both the cell lines respectively**

1. Bevacizumab (Bev)
2. Cetuximab (Cet)
3. Regorafenib (Reg)
4. Panitumumab (Pan)
5. Lenvatinib (Len)
6. 5-FU
7. Folinic Acid (FA)
8. Oxaliplatin (Oxa)
9. Irinotecan (Iri)
10. Gemcitabine (Gem)

AI-PRS based combinatorial drug screening (*in vitro*) for personalized medicine

5. Experimental results

HCT-116	Lenvatinib	5-FU	Irinotecan	Gemcitabine
Mono IC-50 (μM)	28.47	8.561	0.010	0.183
Concentration used in combination (μM)	6.558	4.505	8.027pM	0.033
HT-29	**Lenvatinib**	**5-FU**	**Irinotecan**	**Gemcitabine**
Mono IC-50 (μM)	50.0	13.9	0.1	0.366
Concentration used in combination (μM)	20.0	1.409	1.897	27.9nM

Monotherapy

- Individual drug treatment need higher concentration.
- More toxicity.
- Increased drug resistance.
- Less effective.

AI-PRS combination Therapy

- Combination drug treatment need lower concentration.
- Less toxic.
- Increased drug sensitivity.
- Higher efficacy.

Result and Discussion- AI-PRS Drug Screening

Common top drug combinations



CHEMO Drugs

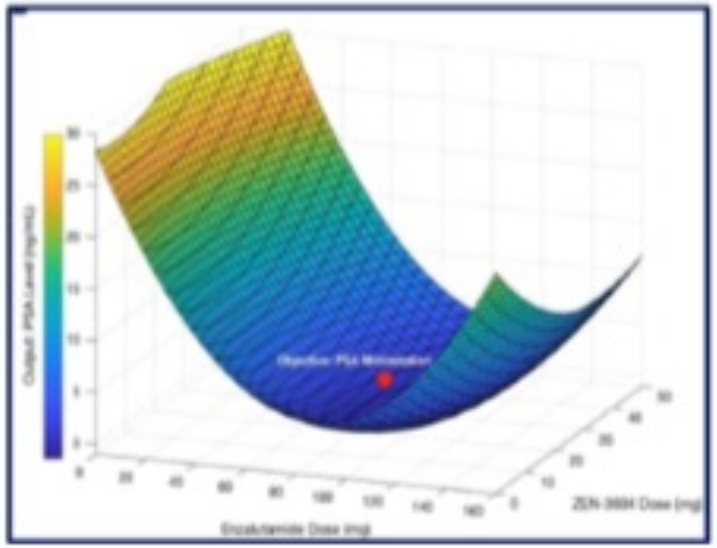
5-FU
Irinotecan
Gemicitabine
Oxaliplatin



Target Drugs

Regorafenib
Cetuximab

AI-PRS



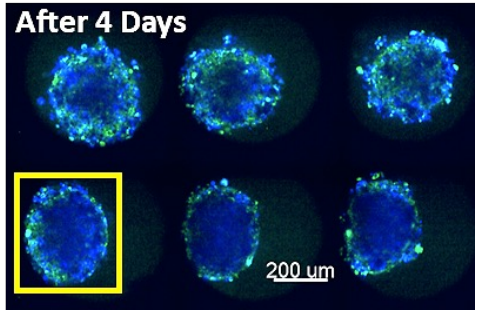


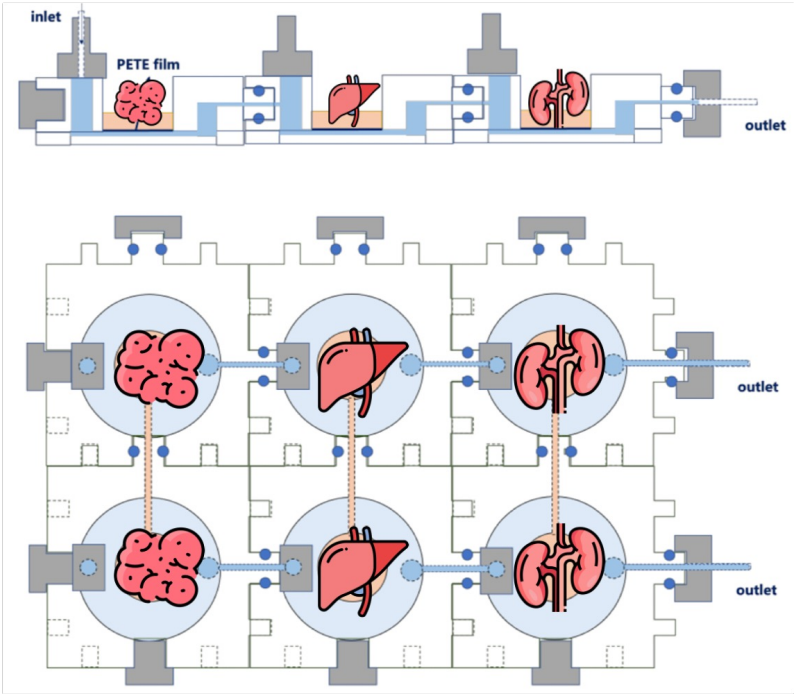
Patients' CTCs in One Month

Rank	Optimized 3-drug combo	Optimized 4-drug combo
1	U+R+C	U+G+R+C
2	U+G+C	U+O+R+C

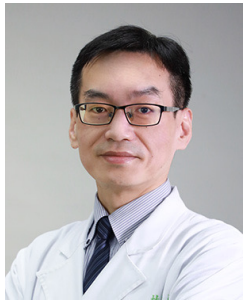
HY Yang et al, Adanced Pharmacuiticals, 2023

Part III: 3-D Tumor and Kidney/Liver Organ on a Chip

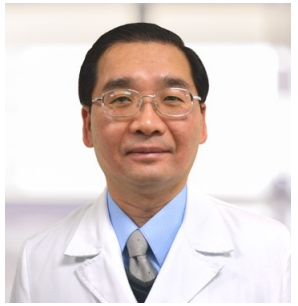








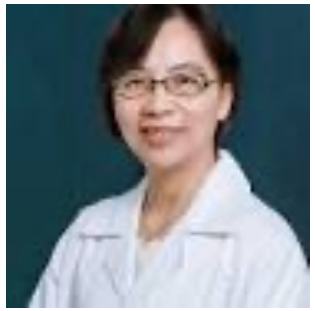
NVGH Dr. CK Chiang,
Dr. CG Lin (CRC Cancer)



NTU H, Dr. CC Ke
(Lung Cancer)

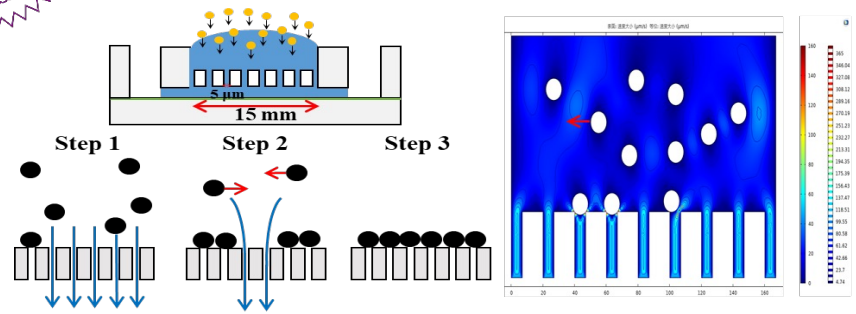


LK-CGH, Dir. Dr. HH
HSU (Nephrology)

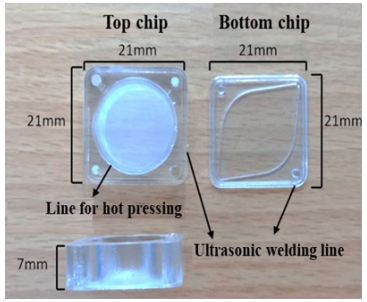


NHRI, DD. Dr. MS Hong
(Pharmaceutical)

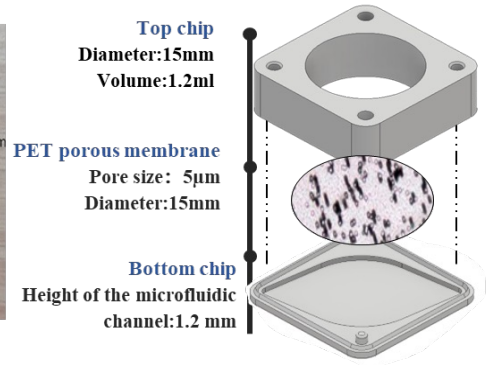
3R (microfluidic) chip (24 wells) and perfusion system



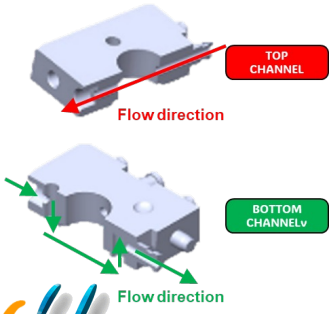
Prototype (the CSDS SACA chip)

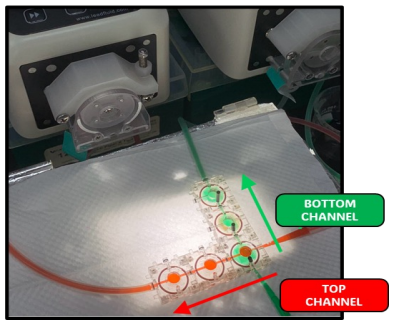


Channel side view

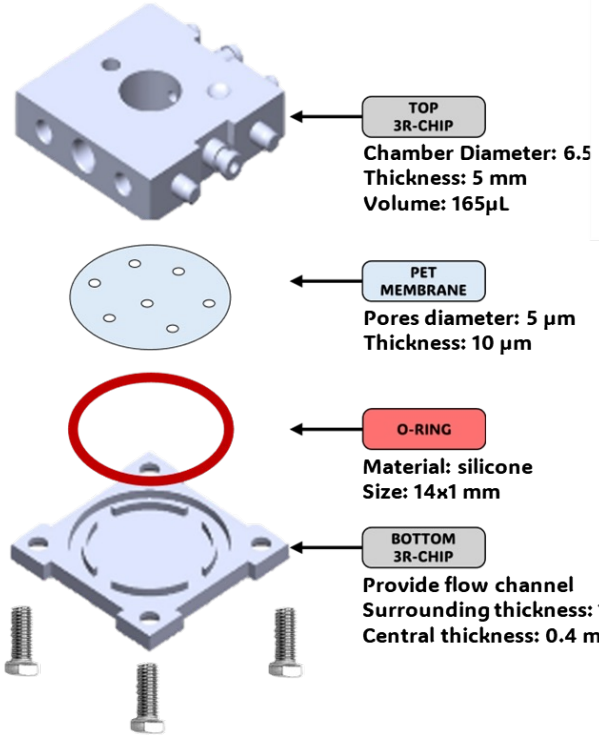


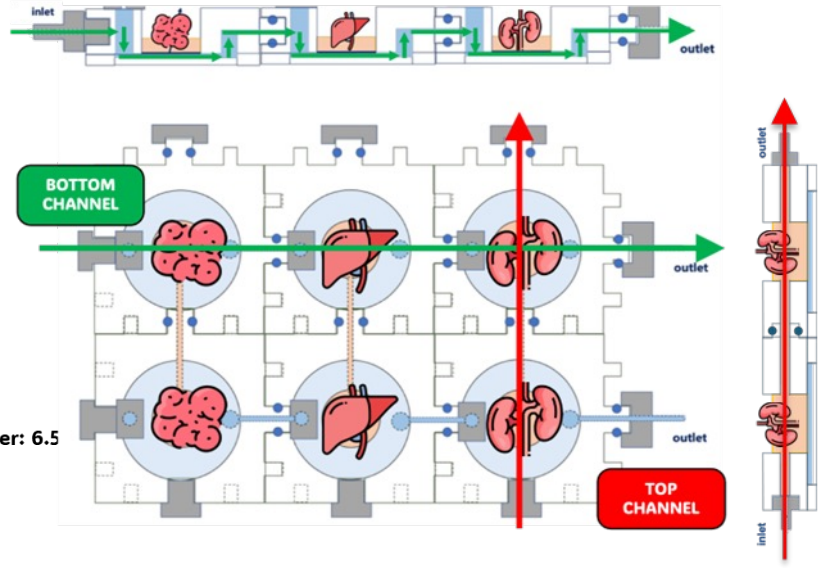
Fluid System Diagram





Exploded Views





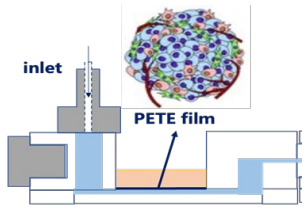
2nd generation of 3R chip array unit and system

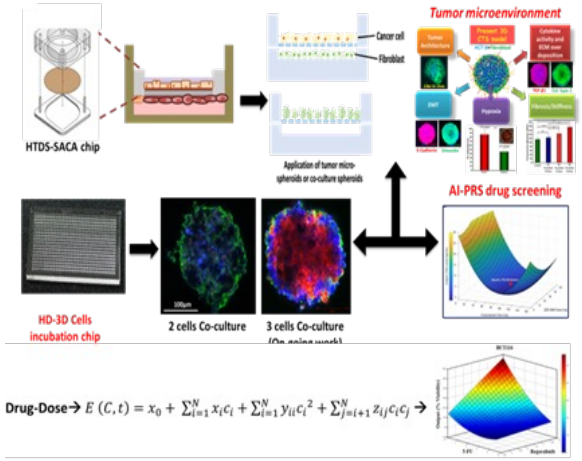
Features:

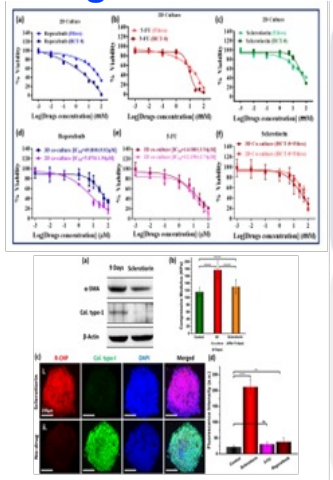
1. Two parts are separated by a semi-permeable membrane as the interface. The upper part simulates the internal tissue, and the lower part simulates the blood circulation and immune environment.
2. Can be observed on a general fluorescent microscope.
3. Can be used for static or dynamic fluid experiments.
4. Can be connected in series to form a linkage relationship and take redundancy into consideration.
5. Nanosensors can be added (e.g O2, pH, Glucose, Lactic Acid, for 3D dynamic measurement of disease information, etc.)

1. Tumor-on chip models

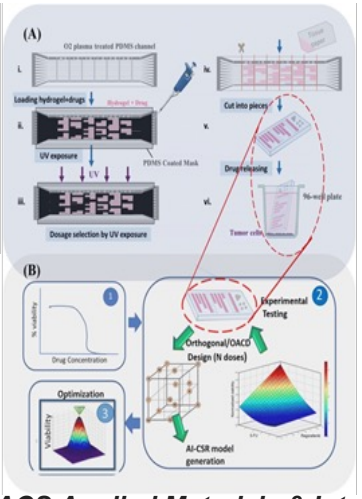
2D/3D dynamic co-culture for drug screening



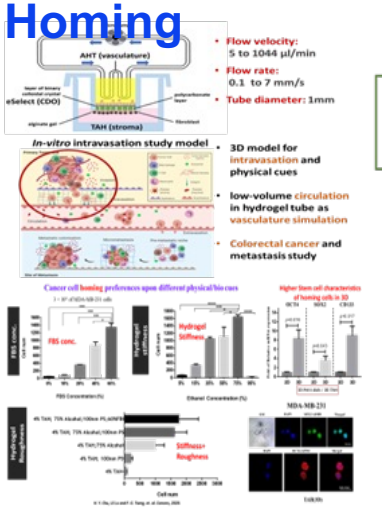




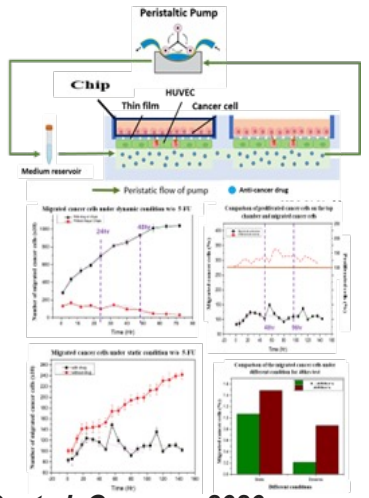
In-parallel Antitumor drug screening



Cancer cell Homing

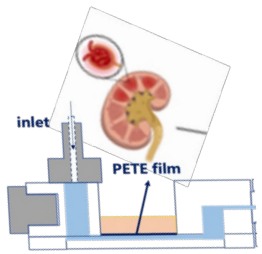


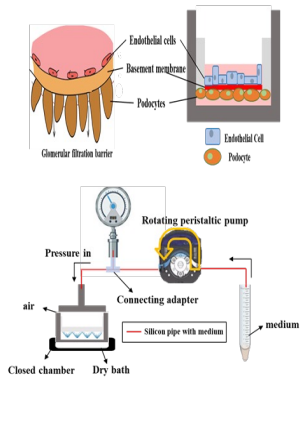
Intravasation/ migration

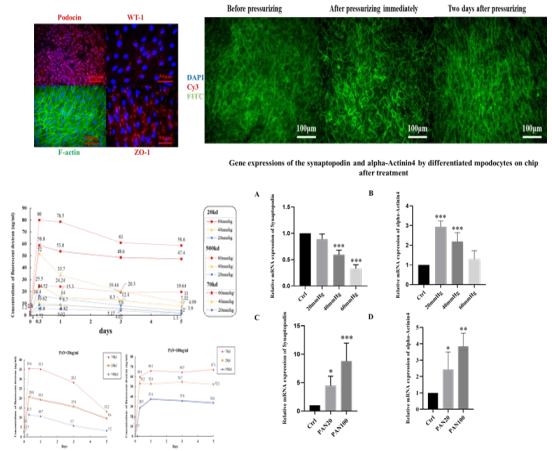


Kaladharan K, Tseng FG. et al. Lab on a Chip. 2024; Goudar VS, Tseng FG. et al. ACS Applied Materials & Interfaces. 2021; Chu HY, Tseng FG. et al. Cancers. 2020

2. Kidney (Glomerular filtration barrier)-on chip platform

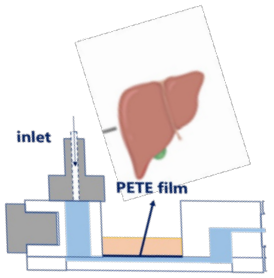


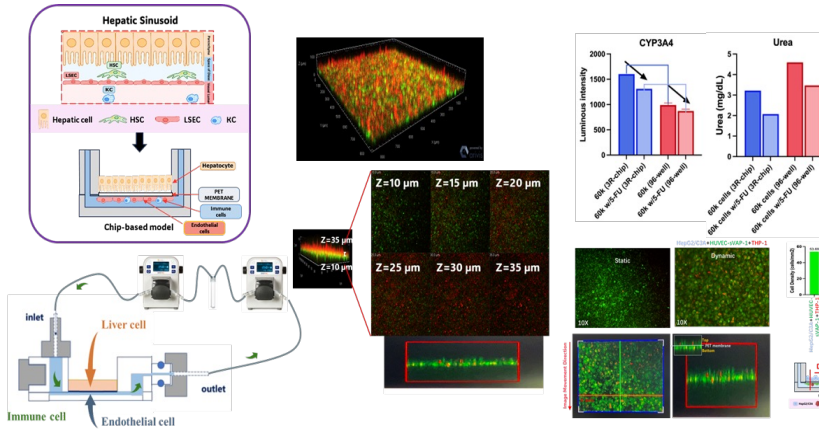




F. G. Tseng, et. al. Micromachines, 2018, 2025

3. Liver (Non-alcoholic steatohepatitis-NASH)-on chip platform





F. G. Tseng, et. al. Analyst, 2026

From Single-Organ-on-a-Chip to Multi-Organs-on-a-Chip

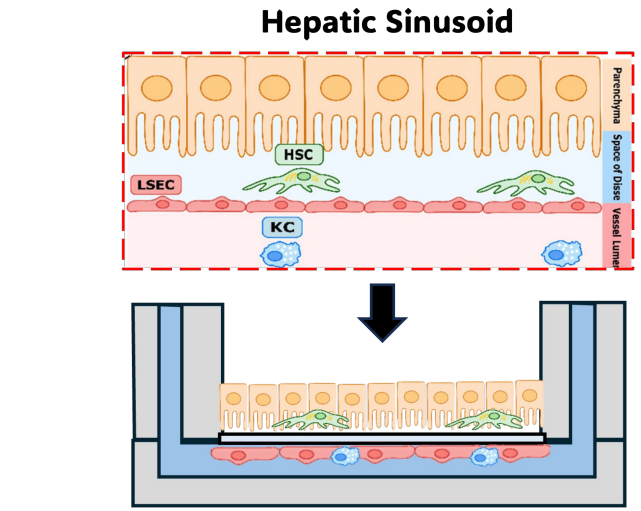
1. Using 3R chip to build single organ on chip models mimicking physiological metabolism and functions.

2.The interaction between co-cultured cells on chip and responses to drugs can be studied.

3. Different single organ on chip models can be connected to form a multi-organ on chip platform.

4. The interaction between different organ/tissue model can be studied.

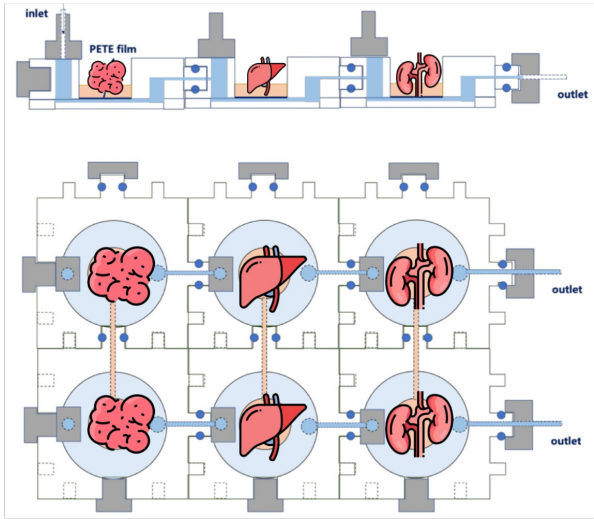
Single-Organ



HepG2-C3A HSC LSEC KC

Aims:
1. Establishment of hepatocyte model and fluidic device.
2. The synthetic and metabolic functions of the liver.

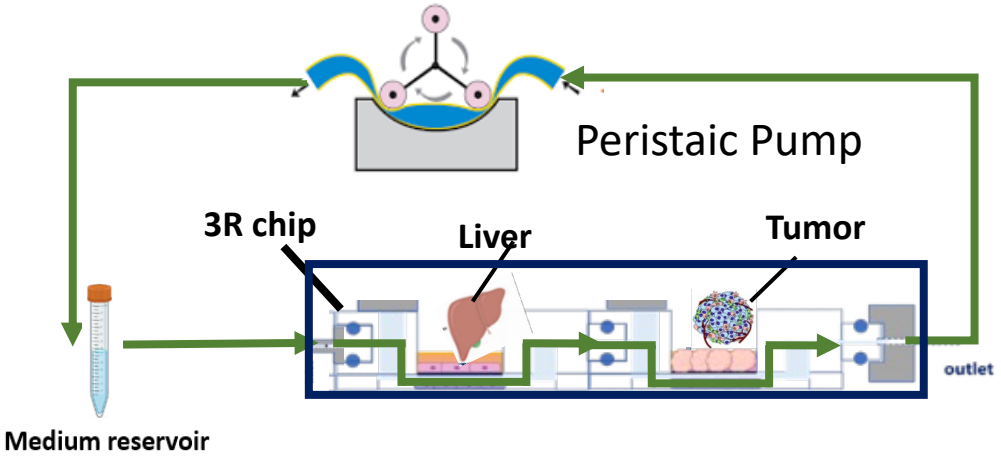
Multi-Organs



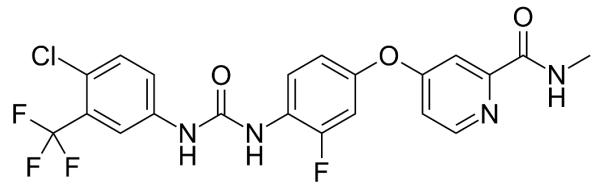
Tumor Liver Kidney

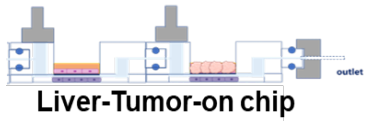
Aims:
1. To connect tumor/ kidney organ models via 3R-chips.
2. Simulate the drug metabolism environment, cancer cell migration and urea filtration.

Tumor-Liver-on chip platform for Regorafenib drug efficacy and safety evaluation



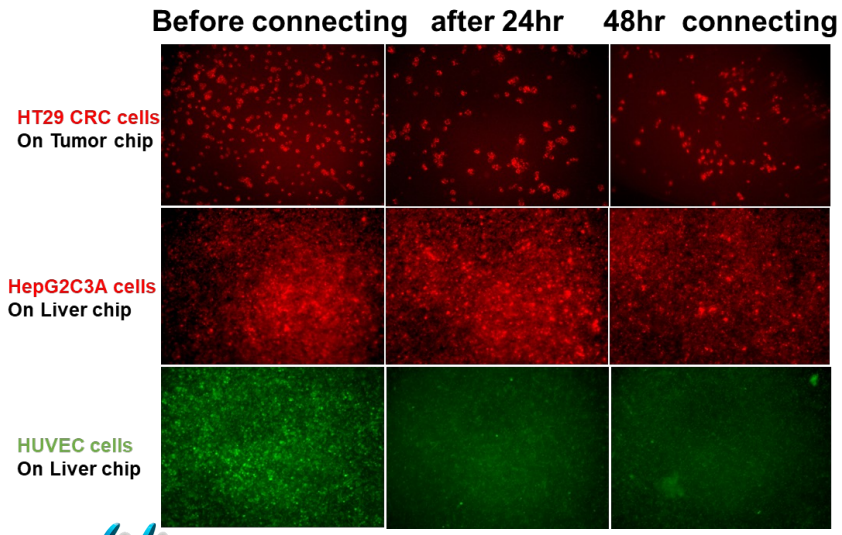
Regorafenib

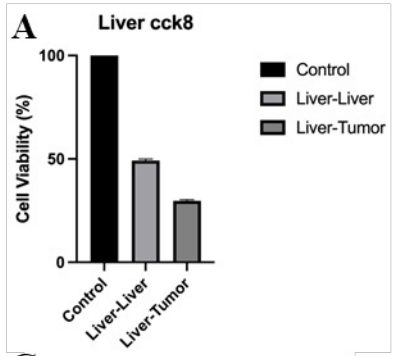


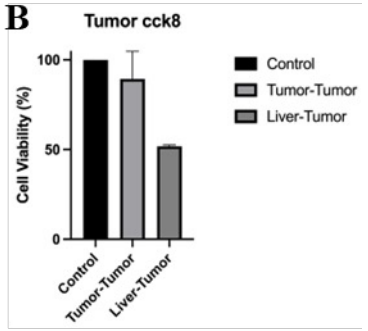


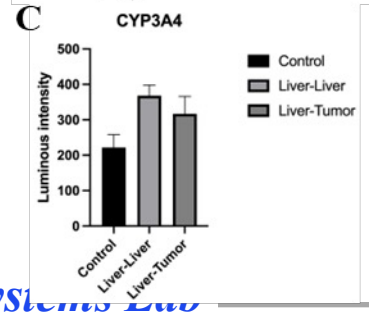
Liver-Tumor-on chip

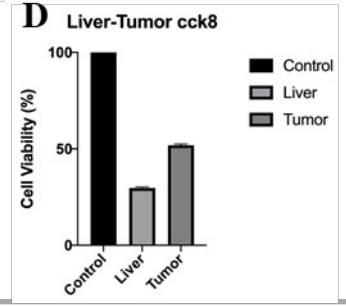
Antitumor drug Regorafenib: 30μM











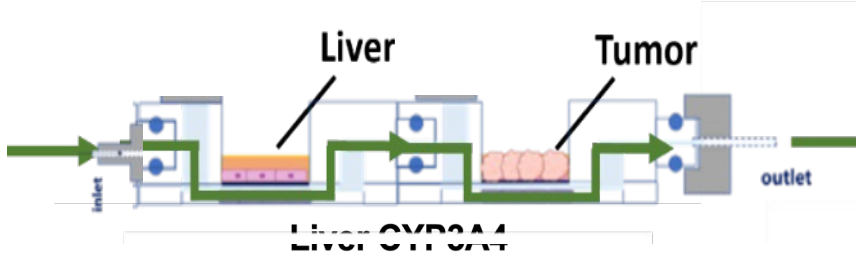
- Establish Liver-tumor on a chip platform
- Evaluate Regorafenib drug efficacy and safety at once
- Adding Kidney chip in the future

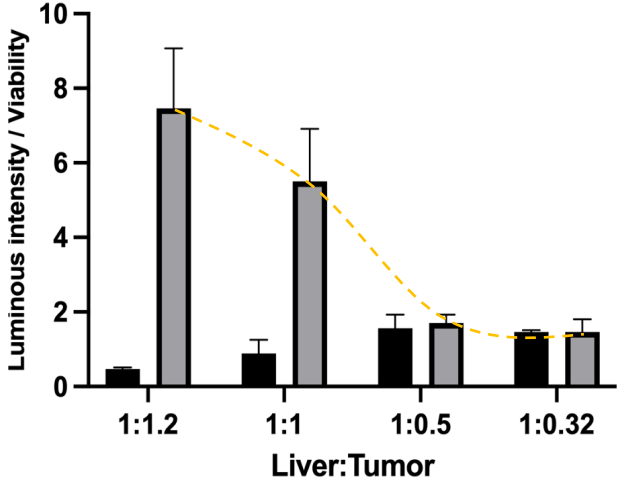
F. G. Tseng, et. al. Analyst, 2026

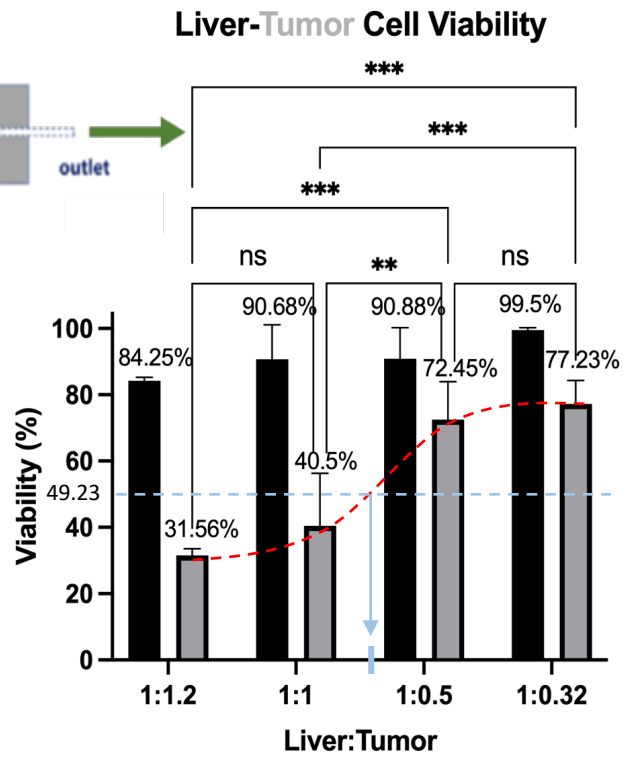
Tumor-Liver-on chip platform for Regorafenib drug efficacy and safety evaluation

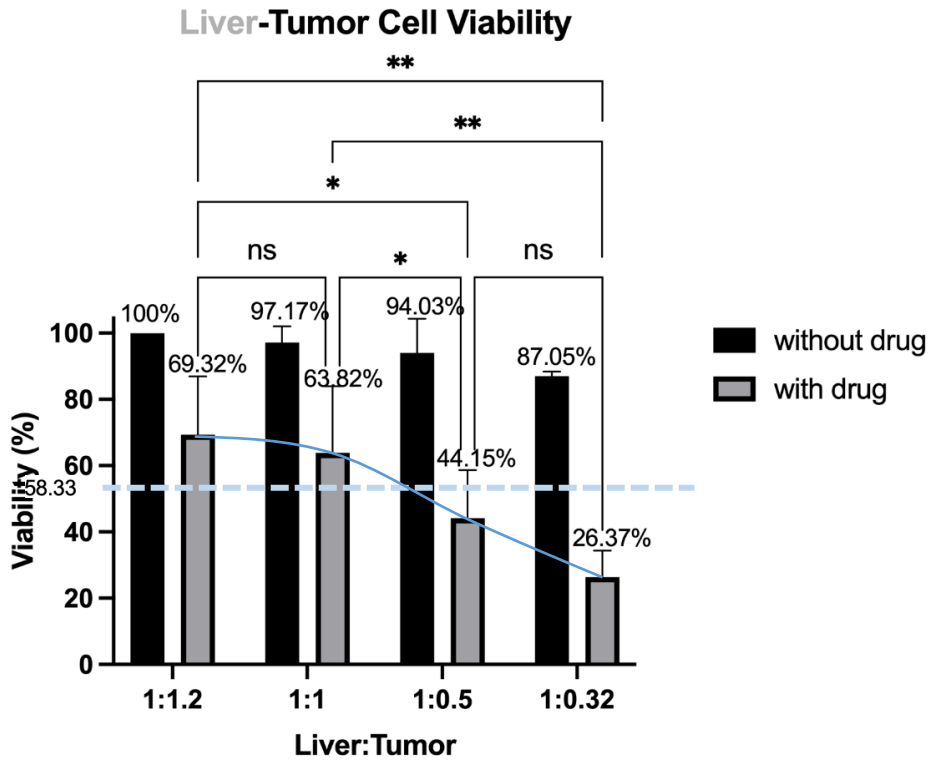
Cell number: HepG2/C3A: 50k /chip Circulation time:24hr

HT-29: 60k,50k,25k,16k /chip Drug: Regorafenib





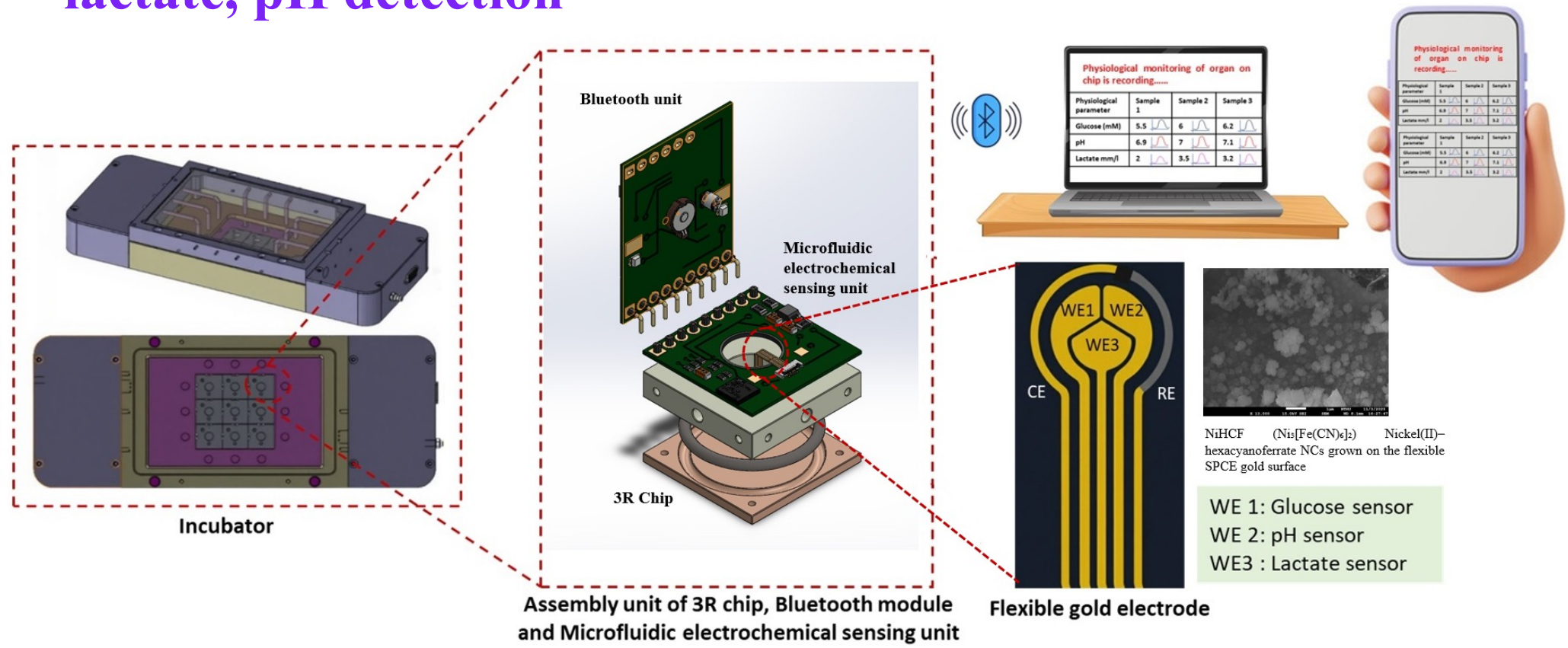




- Drug efficacy on Tumor depends on the tumor to liver loading ratio and the interaction between them.
- When tumor/liver loading lower than 50%, tumor killing rate higher then tumor IC 50.
- When tumor/liver loading higher than 50%, Liver endure higher death rate then liver IC 50, also higher CyP3A4 generation/cell observed.

F. G. Tseng, et. al. Analyst, 2026

Wireless SOC electrochemical sensors array for Oxygen, Glucose, lactate, pH detection



Wireless SoC for Flexible Electrochemical Sensor Array

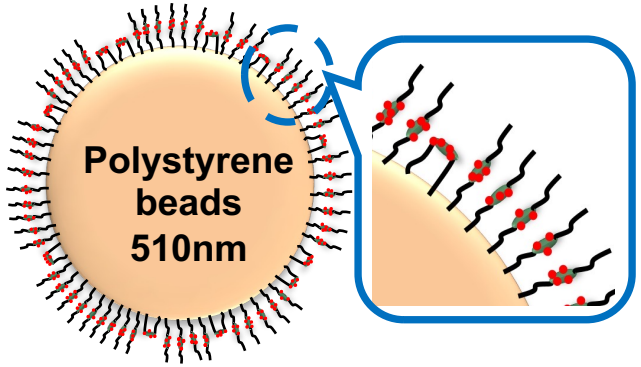
- ✓ **Integrated AFE + BLE: AD5940 with CYBLE222014** enables real-time wireless sensing via Bluetooth.
- ✓ Multi-Analyte Array **3R organ-on-chip** integrates electrochemical sensors (WE1, WE2, WE3, CE, RE) to **measure glucose, pH, and lactate.**
- ✓ **Compact Power Design**: Li-ion battery with ADP162AUJZ regulator for **low-power operation.**
- ✓ Scalable Goal: Toward 27-channel (9×3) flexible array with custom SoC for organ-on-chip monitoring.

Oxygen, Glucose, pH, Temp. Sensitive NPs for Cells Monitoring

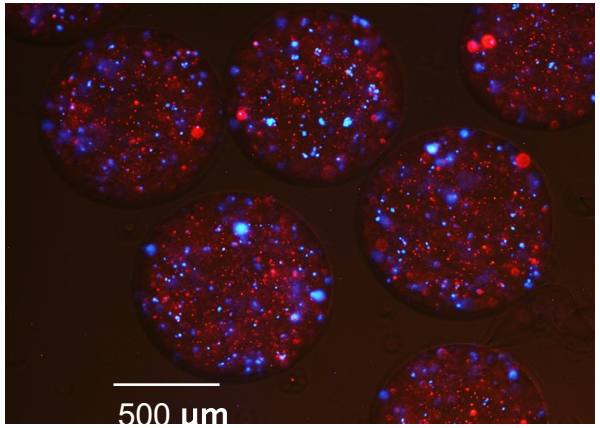
(With MIT Langer's Lab and U. Liverpool Jude's lab)

FNOPs: Dyes **on** PS beads

Manohar et.al., *ACS AMI*, 2018



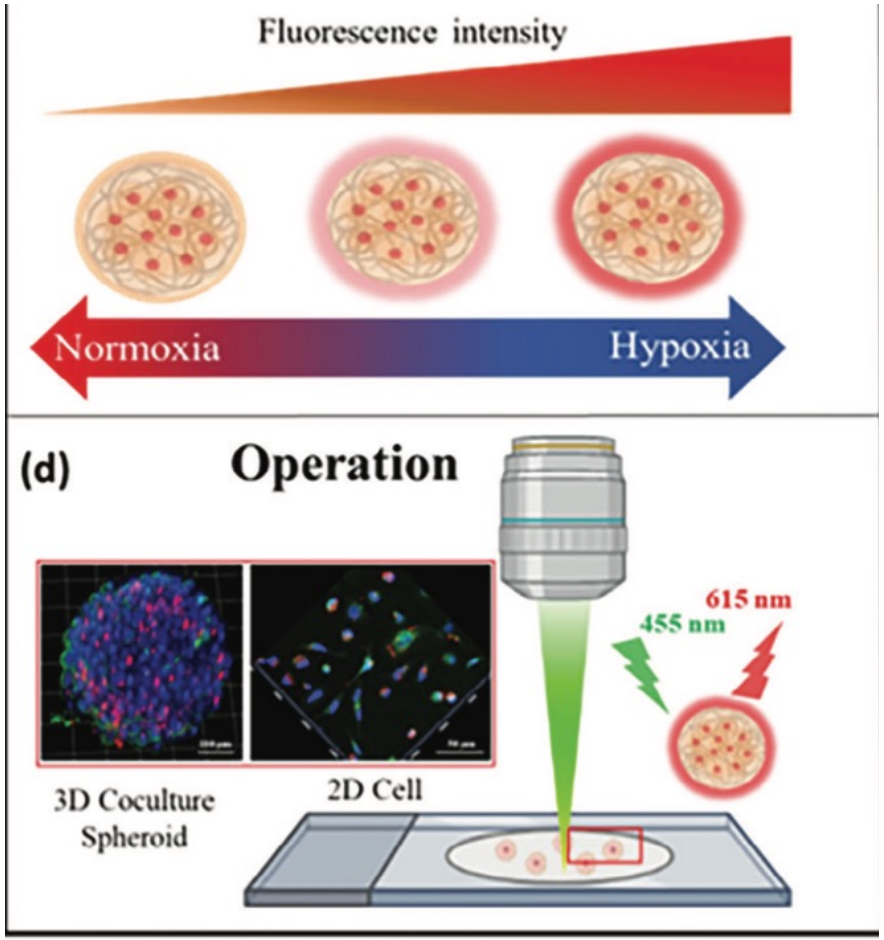
- Pluronic F-127：Linker
- $Ru(dpp)_3Cl_2$：Oxygen (or glucose, pH) sensitive fluorescence dye



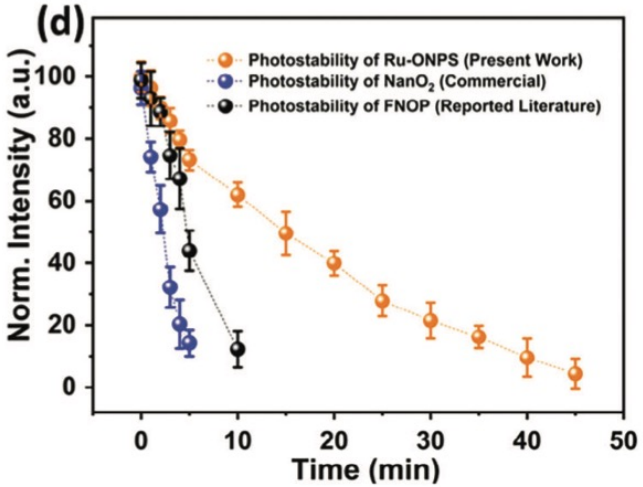
Blue: Hela/DAPI, Red: FNOPs

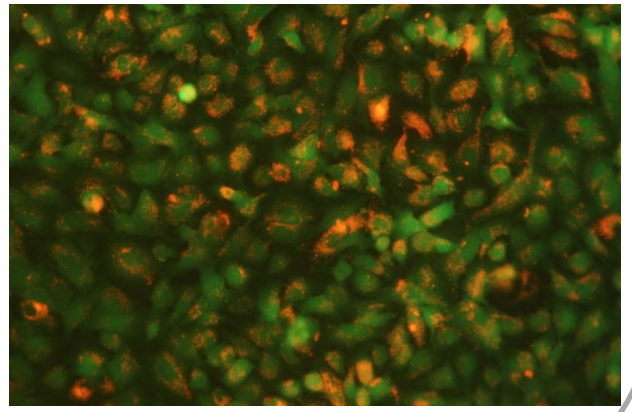
Ru-ONPS:Dyes **inside** Urea-Paraformaldehyde partices

Kumar et.al., *Small*, 2024



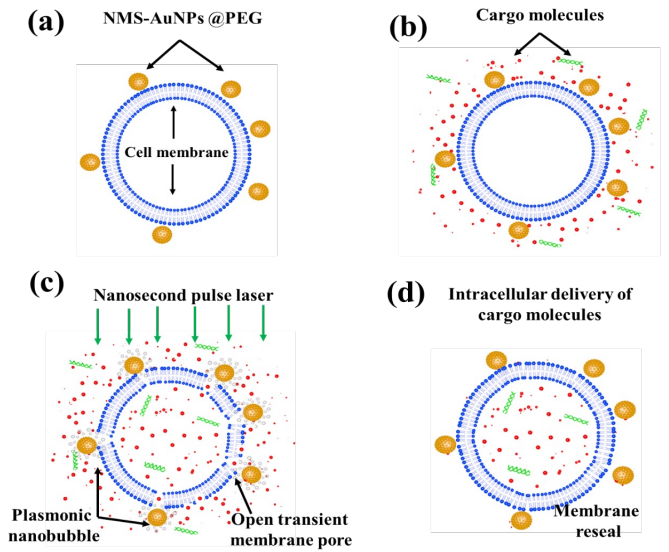
5 times longer Life time for **Ru-ONPS**!!

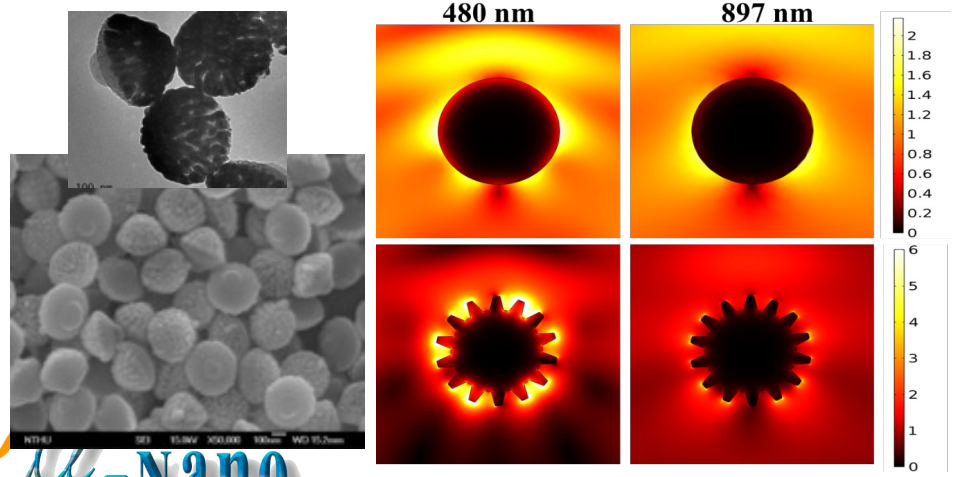




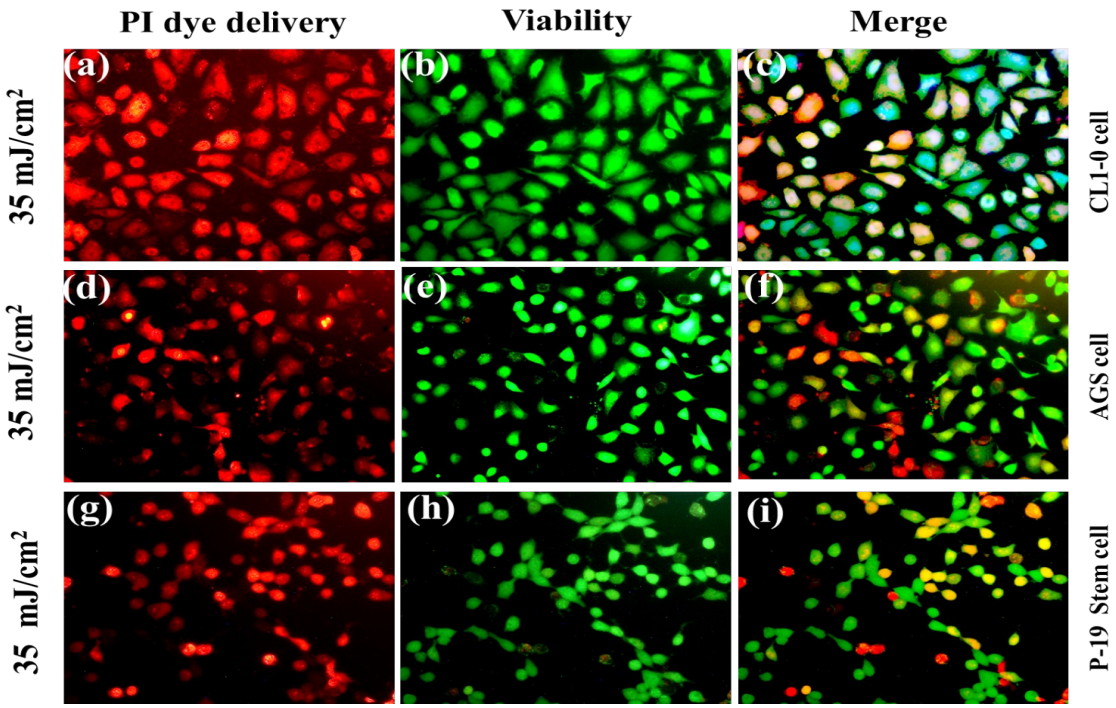
Green: A549 cells/Calcien, Red:FNOPs

Nano-Mushrooms mediated Nano-Second Photoporation





350 nm nano-mushrooms



94% intracellular uptake

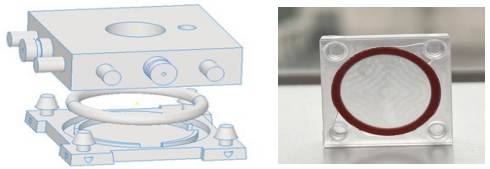
100% cell viability

(35 mJ/cm², 10 ns pulse/10Hz at near infrared ,997 nm)

T. Santra, and FG Tseng, *Analyst 2021, Lab Chip 2020, Cells 2020, ACS Biomater. Sci. Eng.* 2020, *Nanoscale* 2020

Aspect	Our 3R Chip	TissUse Multi-Organ Chip	Emulate Inc. Organ Chip	CN Bio Organ Chip
Design	Highly modular, scalable to **24 co-culture conditions**.	Limited organ combination scalability, no co-culture capability (2 organs × 4 replicates).	Supports multi-organ interaction testing (2 organs × 6 co-cultures).	Supports multi-organ interaction testing (2 organs × 6 co-cultures).
Cell Diversity	Dual-layer co-culture, compatible with **liquid/gas interfaces**, simulating diverse cellular interactions.	Multi-organ co-culture simulates organ interactions, but **no gas interface** (limits lung applications).	Single-organ culture, unable to simulate multi-organ interactions.	Single-organ culture, unable to simulate multi-organ interactions.
Microenvironment	**3D microenvironment** with dynamic perfusion system.	3D microenvironment with microfluidic system.	2D/3D microenvironment with microfluidic system.	2D/3D microenvironment with microfluidic system.
System Integration	Highly integrated: combines **optical observation + microfluidics** for real-time monitoring during culture, suitable for mass production.	Poor integration: bulky chip size, requires post-culture microscopy (no real-time monitoring).	Poor integration: bulky chip size, requires post-culture microscopy (no real-time monitoring).	Standard plate-sized chip; real-time monitoring requires expensive modules.
IP Portfolio	Patents cover **organ chips + real-time culture monitoring systems**.	Patents focus on organ chip design.	Patents focus on organ chip design.	Patents focus on organ chip design.
Market Competitiveness	**Commercialization-ready**: aligned with end-user applications from concept stage.	Primarily suited for academic research.	Primarily suited for academic research.	Primarily suited for academic research.

NTHU 3R chip









Our 3R chip has multiple advantages:
It has significant advantages in combinatorial design, multi-organ interaction simulation, automated system integration and commercialization potential, which is suitable for commercial applications that require high flexibility and scalability.

Summary

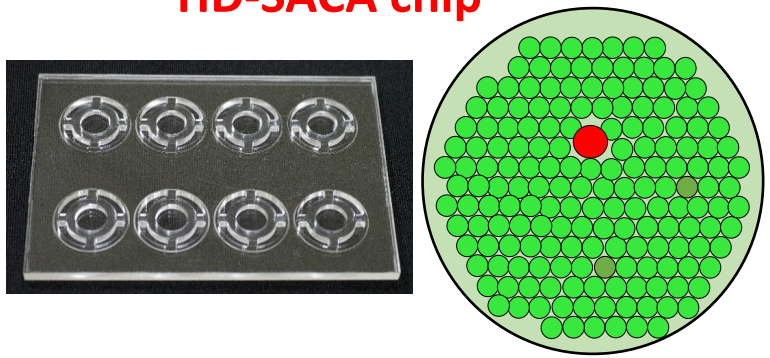
MicroFluidic Systems enabled:

Part I: HD-SACA systems for CTC/CTM identification for Cancer prognosis

Part II: AI-PRS drug screening for precision medicine

Part III: 3D Tumor and Kidney/Liver Organ on a Chip

HD-SACA chip



AI-PRS drug screening

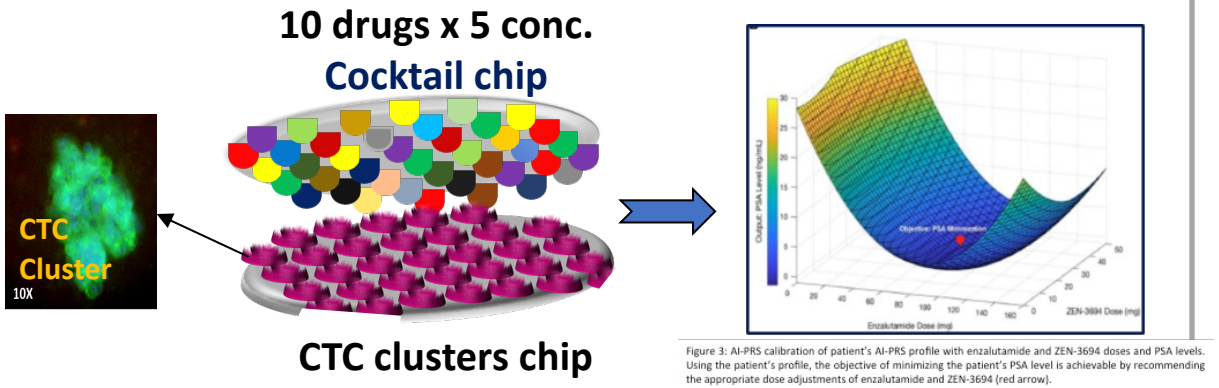
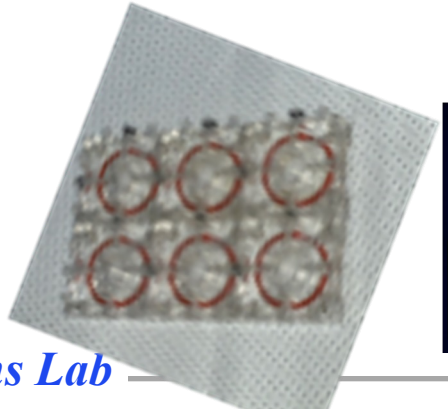
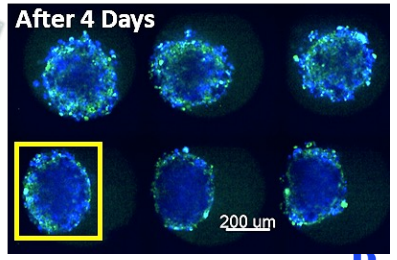
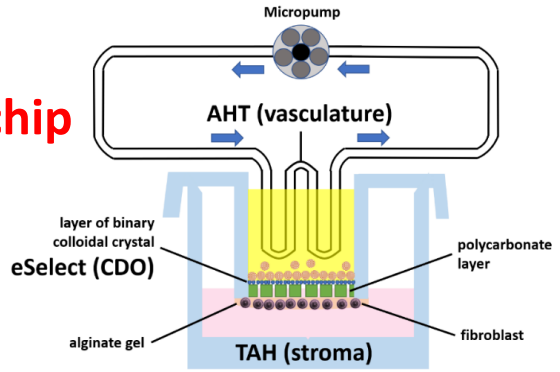


Figure 3: AI-PRS calibration of patient's AI-PRS profile with enzalutamide and ZEN-3694 doses and PSA levels. Using the patient's profile, the objective of minimizing the patient's PSA level is achievable by recommending the appropriate dose adjustments of enzalutamide and ZEN-3694 (red arrow).

3D Tumor & Organoid on a chip







Acknowledgements

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1. NSTC Integration project
2. Shekelton Project, MOST ,Taiwan
3. National Nanotechnology project, MOST, Taiwan
4. Biomedical and Pharmaceutical National Project Program, MOST, Taiwan
5. VUST Interdisciplinary Project, Taiwan
6. National Health Research Institutes, NHRI, Taiwan
7. NTHU Toward Excellent University Project.

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National Health Research Institute, Taiwan
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Dr. MS Hong

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Prof. HY Chang
Prof. DR Yao
Prof. YC Su

North Veteran General Hospital, Taiwan
Dir. CK Chiang,CG Lin (CRC)
Dr. CY Yang (Cancer Biologist)

Taipei Medical University,Taiwan
President Y. Yen (Colon Cancer, Precision medicine) VP KY. Lee (Lung cancer) ,Dean CF Chiu/Dr. LS Liu, (Breast Cancer, Radiology) Dean HB Kuo/Dr. SS Hsiao (lung cancer)

Chang Gung Memorial Hospital, Linkou
Dir. Dr. HH HSU (Nephrology)

THANK YOU Very Much!

NTHU ESS

μ-Nano Bio & fluidic Systems Lab

