TMU-Research Center of Urology and Kidney

Monthly Meeting

Times：2024/1/19(Friday) 14:00-15:00

Google meet link： https://meet.google.com/ias-vbwh-hrq

Meeting Chairperson：Kuan-Yu Hung

Participant：

【TMUH】Ming-Che Liu、Yao-Chou Tsai、Shauh-Der Yeh、Chien-Chih Wu、Hsiao-Yu Lin、Jeng-Cheng Wu、Ching-Hsin Chang、Wei-Chieh Chen、Fang-Yu Ku、Shih-Hsiu Lo、Te-Chao Fang、Hsi-Hsien Chen、Yen-Chung Lin、Yueh-Lin Wu、Chih-Chin Kao、Ching-Yi Chen、Shu-Ching Yeh、TING-EN TAI

【WFH】Yu-Ching Wen、Liang-Ming Lee、Ke-Hsun Lin、Yung-Wei Lin、Chi-Hao Hsiao、Syuan-Hao Syu、Chung-Howe Lai、Chih-Chen Hsu、Tso-Hsiao Chen、Yuh-Mou Sue、Chung-Yi Cheng、Chung-Te Liu、Yun-Hong Yang、Ming-Che Lee、Cho-Hsing Chung

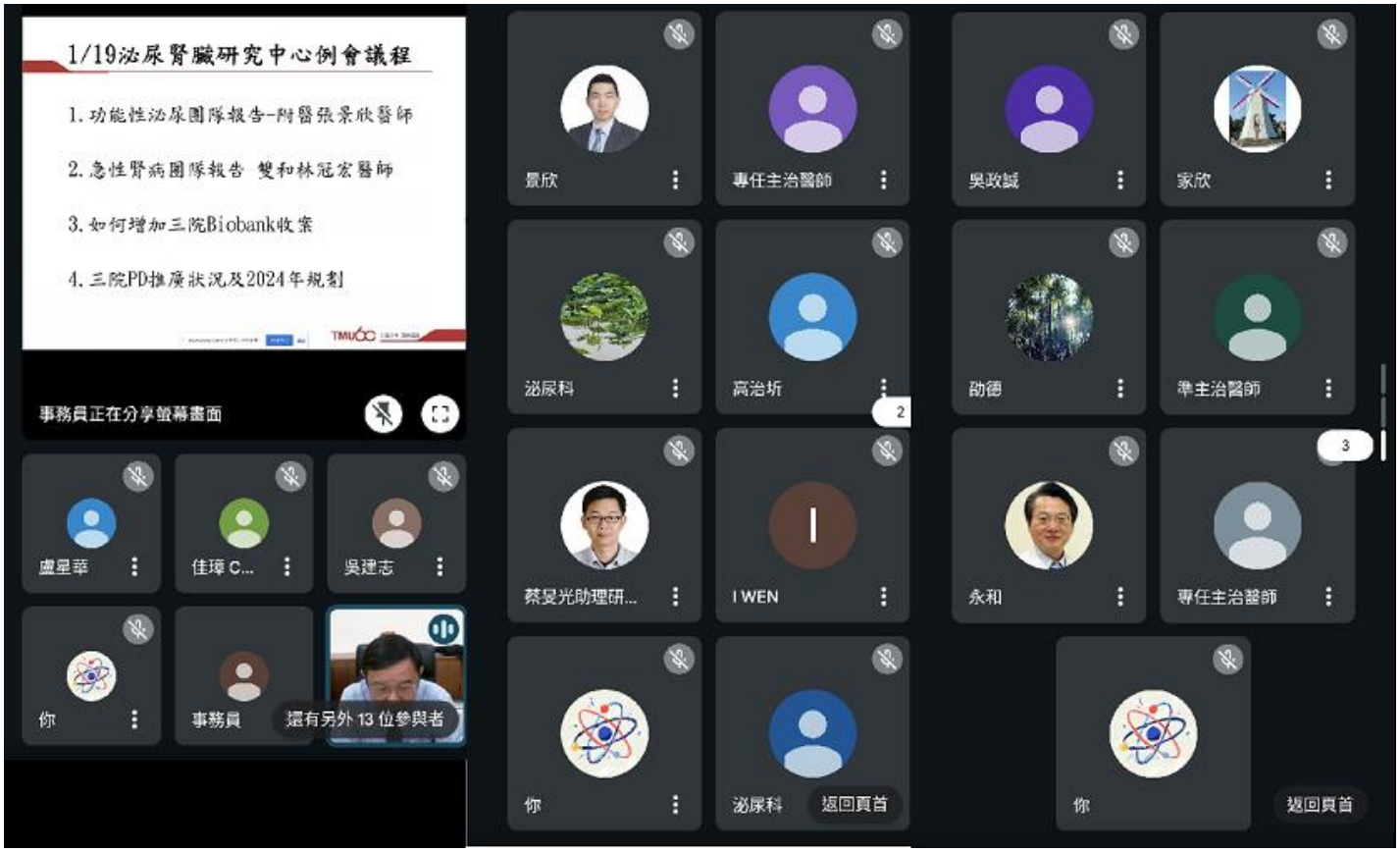
【SHH】Mai-Szu Wu、Chia-Chang Wu、Chia-Hung Liu、Yi-Te Chiang、Kai-Yi Tzou、Wei-Tang Kao、Su-Wei Hu、Wen-Ling Wu、Mei-Yi Wu、Lie-Yee Hung、Cai-Mei Zheng、I-Jen Chiu、Yu-Wei Chen、Chia-Te Liao、Cheng-Hsien Chen、Hui-Wen Chiu、Po-Han Yu、I-Wen Wu、Tze-Wah Kao、Kuan-Hung Lin

【SKMH】Yung-Ho Hsu、Chu-Lin Chou

Chief：Mai-Szu Wu (President, TMU)、Yen-Hua Huang (Dean, Research and Development, TMU)、Chih-Cheng Hsu (Professor, NHRI)、Ke-Hung Tsui (Vice President, SHH) 、Shing-Hwa Lu

Agenda： 1. Functional urological team

2. Acute kidney disease team



U-NEURON
永立榮生醫 羊水幹細胞專家

UA002 (Allogeneic Amniotic Fluid Stem Cells) in Patients with Radical Prostatectomy (RP)- or Diabetes Mellitus (DM)-Associated Erectile Dysfunction (ED)

UA002 羊水幹細胞在RP or DM ED病人之臨床試驗介紹

請轉介ED病人到 附醫泌尿 張景欣

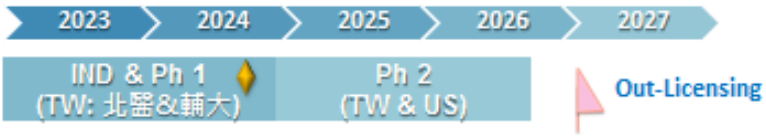
永立榮生醫股份有限公司
U-NEURON BioMed Inc.

www.en.u-neuron.com

羊水幹細胞治療神經性勃起功能障礙臨床試驗

- **Study Title:** An Open-Label, Non-Randomized, Dose-Escalation Phase I Study to Evaluate the Safety of UA002 **(Allogeneic Amniotic Fluid Stem Cells)** in Subjects with **Diabetes Mellitus (DM)- or Radical Prostatectomy (RP)-Associated Erectile Dysfunction (ED)**

- **試驗時程:**



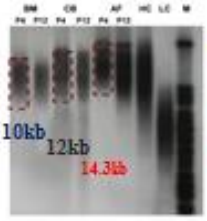
- **本試驗的的特點與競爭性:**
  - ◆ **羊水幹細胞:**
    1. **台灣原創的幹細胞 (發明人: 永利榮生醫總經理黃效民博士)**
    2. **最年輕，分化能力最強的幹細胞 (端粒最長，可分裂最多次)，且沒有道德倫理議題**
    3. **異體幹細胞，可量產商化**
    4. **可分化為外胚層，有神經修復的能力 (針對口服藥無效的神經性勃起功能障礙)**
  - ◆ **試驗設計:**
    1. **有競爭性的適應症:** 針對神經性勃起功能障礙，目前僅韓國一家廠商(自體骨髓幹細胞)進入臨床二期
    2. **具國際性:** 臨床二期將於**美國&台灣**收案

U-NEURON
永立榮生醫 羊水幹細胞專家

羊水幹細胞 (MSC 4.0)

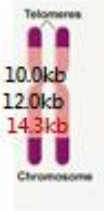
羊水幹細胞的絕對優勢

時代雜誌(2007)票選：
羊水幹細胞為十大醫學突破之一



(生理時鐘)
DNA的端粒最長

BM:骨髓幹細胞 10.0kb
CB:臍帶血幹細胞 12.0kb
AF:羊水幹細胞 14.3kb



人類羊水幹細胞 (唯一具備三個胚層)
『誘導再生已發表文獻』

外胚層：神經細胞 、多巴胺神經細胞、腦中風改善。
中胚層：脂肪細胞、 成骨細胞、 軟骨細胞、 心肌細胞、 心臟瓣膜、血管內皮細胞。
內胚層：肝臟細胞、橫隔膜與氣管的組織細胞。

黃效民博士
幹細胞領域研究與應用權威
帶領跨國再生醫學菁英成員,結合國家級的細胞儲存中心打造出亞洲幹細胞應用最權威的團隊

國際第一篇羊水幹細胞論文
美國專利證號為7,101,710B

confidential

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U-NEURON

羊水幹細胞ED動物結果

永立榮與輔大醫學系合作 將進軍性功能障礙療法市場

經濟日報 | 2023年07月03日

永立榮生醫今（3）日表示，與輔大醫學系合作，針對其臨床...

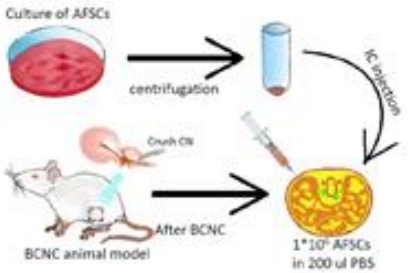
永立榮生醫今（3）日表示，與輔大醫學系合作，針對其臨床前產品UA002進行動物試驗，證實UA002可有效修復海綿體神經、血管內皮與平滑肌細胞，進而改善勃起功能。永立榮將進行後續的臨床試驗，進軍龐大的性功能障礙療法市場。

永立榮另一項可治療退化性疾病的UA001，也已經取得台灣衛福部食品藥物管理署（TFDA）的膝蓋退化性關節炎的Phase I/II的臨床試驗許可（IND）。公司的羊水幹細胞產品線，已儼然成形。

永立榮表示，該公司與輔仁大學醫學系研究團隊合作，透過動物試驗，驗證從懷孕期羊水分離培養出的羊水幹細胞，確實具改善神經受損導致男性勃起功能障礙的潛力，並於6月10-11日在林口長庚醫院舉辦的「台灣男性醫性學醫學會」的論文發表與專題演講會中，發表其研究結果。（請見連結：https://ppt.cc/fskdOx）。

根據輔大醫學系吳宜娜副教授團隊的研究結果，以動物海綿體神經損傷後之勃起功能障礙模型，所進行的動物生理功能與病理試驗結果顯示，羊水幹細胞確實有效修復海綿體神經、血管內皮與海綿體平滑肌細胞的功能，進而改善勃起功能障礙。

有別於目前市面上藉由血管舒張達到短暫勃起之藥物，對於神經受損修復幾乎無效的狀況，羊水幹細胞展現出回復神經組織的潛力，證明其確實具備進一步開發成男性勃起功能障礙新療法的價值。



羊水幹細胞於動物陰莖海綿體注射治療後

1. 動物電生理實驗:
   - 勃起功能之硬度與持久度改善
2. 海綿體組織切片:
   - 神經萎縮改善
   - 血管內皮細胞萎縮改善
   - 平滑肌細胞萎縮改善

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Study Overview

Indication	Diabetes Mellitus (DM)- or Radical Prostatectomy (RP)-Associated **Erectile Dysfunction (ED)**
Study Design	Open-label, 3 + 3 dose-escalation, and dose-expension study
Phase	**I**
Study site:	**Multiple** sites in Taiwan
Study Intervention	A single intracavernous injection of **UA002 (Allogeneic Amniotic Fluid Stem Cells)**
Study Population	Subjects aged 18~75 years old with DM- or RP-associated ED

Objectives (1/2)

OBJECTIVES	ENDPOINTS
Primary	
1. To assess the safety and tolerability of UA002 in subjects with DM- or RP-associated ED 2. To determine the maximum tolerated dose (MTD) of UA002 based on dose-limiting toxicity (DLT) observation in subjects with DM- or RP-associated ED	1. Incidence of dose-limiting toxicity (**DLT**) for maximum tolerated dose (**MTD**) evaluation, and change from baseline to post-treatment visits in **vital signs**, 12-lead electrocardiogram (**EKG**), and laboratory parameters, prostate specific antigen (**PSA**) level (**for the RP subjects only**), panel reactive antibody (**PRA**) level, and the number of subjects abnormal finding of **physical examination** and **chest X-ray** 2. Incidence of adverse events (**AEs**), AEs of special interest (**AESIs**), and serious adverse events (**SAEs**) up to 52 weeks 3. Incidence of **immediate AEs**

Objectives (2/2)

OBJECTIVES	ENDPOINTS
Secondary	
1. To assess the preliminary efficacy of UA002 in subjects with DM- or RP-associated ED	1. Change from baseline to post-treatment visits in the score of International Index of Erectile Function (**IIEF**) 2. Change from baseline to post-treatment visits in Erection Hardness Score (**EHS**) 3. Change from baseline to post-treatment visits in Sexual Encounter Profile (**SEP**) 4. The percentage of responders of Global Assessment Questions (**GAQ**) at post-treatment visits 5. Change from baseline to Visit 7 (Day 169) and Visit 9/EOS (Day 365) in peak systolic velocity (**PSV**) and end-diastolic velocity (**EDV**)

Inclusion Criteria (1/3)

For all subjects

1. Male aged ≥ 18 and ≤ 75 years old
4. Who is willing to engage in sexual activity **at least twice per month** during the study
5. With a total testosterone level ≥ 200 ng/dL at the screening visit
6. Who does not satisfy sexual activity with proper sexual stimulation in spite of taking **maximum dose of oral PDE5 inhibitor within last 8 weeks** prior to the screening visit, or who is unwilling or unsuitable for **standard treatment other than PDE5 inhibitor** (including intracavernous injection vasoactive agents and/or vacuum constriction device (VCD))
7. If the subject has taken α-blocker, the frequency and the dosage should be stable for more than 12 weeks prior to the screening visit
8. Subject has signed informed consent
9. Willingness and ability to comply with protocol-stated requirements, instructions, and restrictions in the investigator's judgement

Inclusion Criteria (2/3)

2. For the subject with **diabetes mellitus (DM)**:
   a. Diagnosed with type 1 or type 2 DM
   b. Has received and is willing to continue to receive treatments for DM
   c. **HbA1c between 6.5~10%** at the screening visit
   d. With EF domain of IIEF5 score between 11~22 at the screening visit
   e. Has **never received radical prostatectomy (RP)**
   f. ED history < 3 years
   g. Diagnosed with ED **at least 12 weeks** prior to the screening visit

Inclusion Criteria (3/3)

3. For the subject with **radical prostatectomy (RP)**:
   a. **Prior to RP**, the subject had
      - **Normal** erectile function or **mild** ED (judged by the investigator retrospectively at the screening visit)
      - With **localized prostate cancer**: prostate specific antigen (PSA) < 20 ng/mL, pathological Gleason score grade 1 (Gleason score sum ≤ 6 (3+3)) or 2 (Gleason score sum 7 (3+4)), pathological stage ≤ T2 (N0, M0)
   b. Received **RP within 12 to 52 weeks** prior to the screening visit
   c. With PSA ≤ 0.2 ng/mL and without additional radiotherapy or hormone therapy after RP
   d. With EF domain of IIEF score between 11~22 at the screening visit
   e. **HbA1c < 6.5%** at the screening visit

Efficacy Assessments

- International index of erectile function (IIEF)
- Erection hardness score (EHS)
- Global assessment question (GAQ)
- Sexual encounter profile (SEP)
- Duplex Doppler ultrasonography

Safety Assessments

- Incidence of dose-limiting toxicity (**DLT**) for maximum tolerated dose (**MTD**) evaluation, and change from baseline to post-treatment visits in **vital signs**, 12-lead electrocardiogram (**EKG**), and laboratory parameters, prostate specific antigen (**PSA**) level (**for the RP subjects only**), panel reactive antibody (**PRA**) level, and the number of subjects abnormal finding of **physical examination** and **chest X-ray**
- Incidence of adverse events (**AEs**), AEs of special interest (**AESIs**), and serious adverse events (**SAEs**) up to 52 weeks
- Incidence of **immediate AEs**

臺北醫學大學
泌尿腎臟研究中心

急性腎病團隊

報告人：林冠宏 醫師

Outline

- AKI alert system and clinical application
- Multi-omics research investigating molecular signature of septic AKI

數位醫療

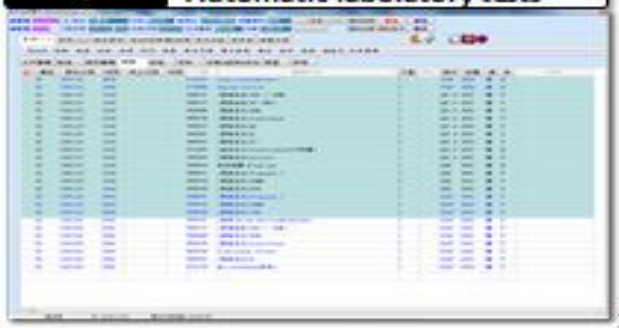
AKI eAlert system & AKD tracking system

1 Electronic alert of AKI

2 AKI care bundle

3 AKI care bundle embed in HIS

4 Automatic laboratory tests

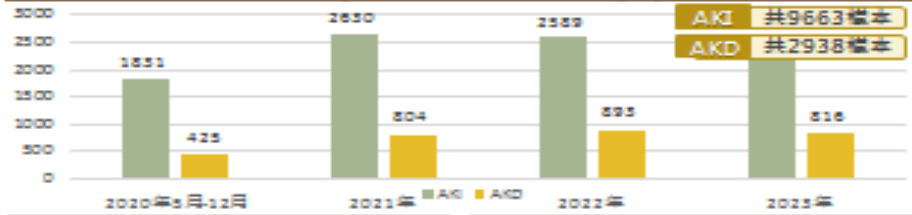


AKI, acute kidney injury

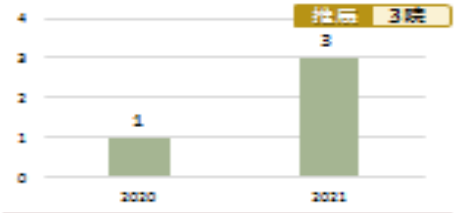
急性腎病概況

年度 2023　季度 全部

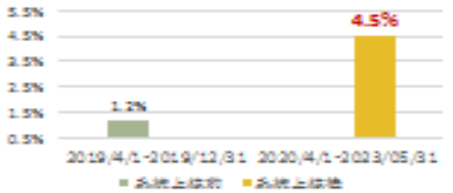
AKI eAlert system & AKD tracking system



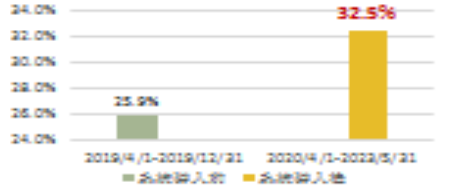
Databases of AKI-AKD research



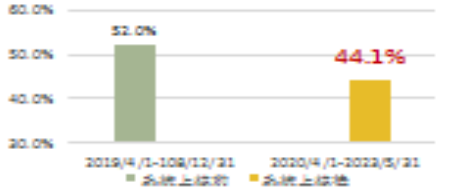
出院診斷AKI比率



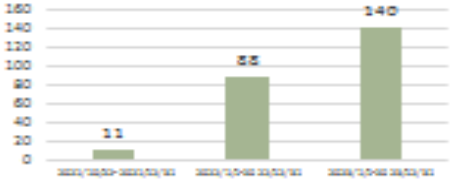
AKI回診腎臟科比率



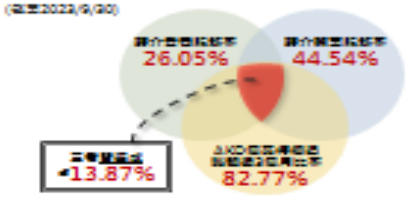
AKI發生後120天內有NSAID用藥紀錄比率



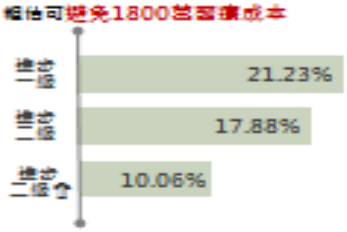
AKD收案管理人數(累積個案239人)



團隊介入照護



AKD後DALYS(eGFR < 45)



3B的實踐：Bench-Bedside-Business

1

專利申請中
(已通過北醫大審查)

經濟部
智慧財產局

2

2023年 第二十屆
國家新創獎-臨床新創獎

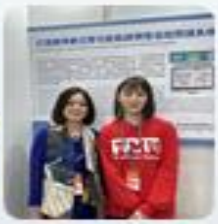
2022年 NHQA

2021年 SNQ

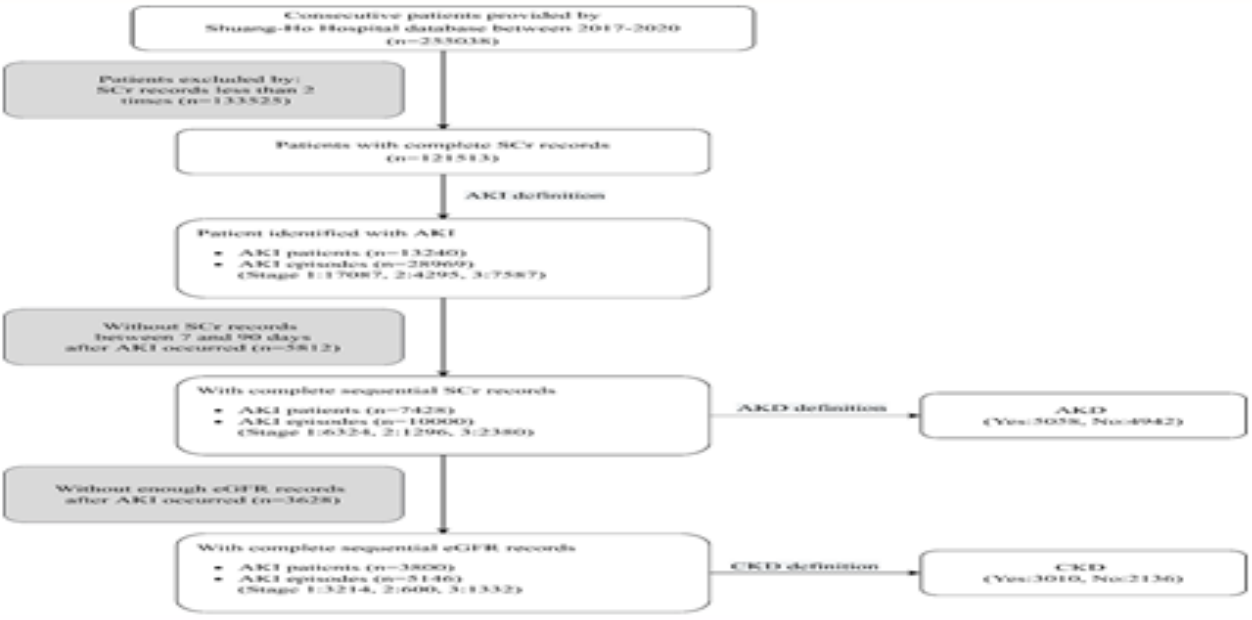
3

Healthcare EXPO TAIWAN 台灣醫療科技展

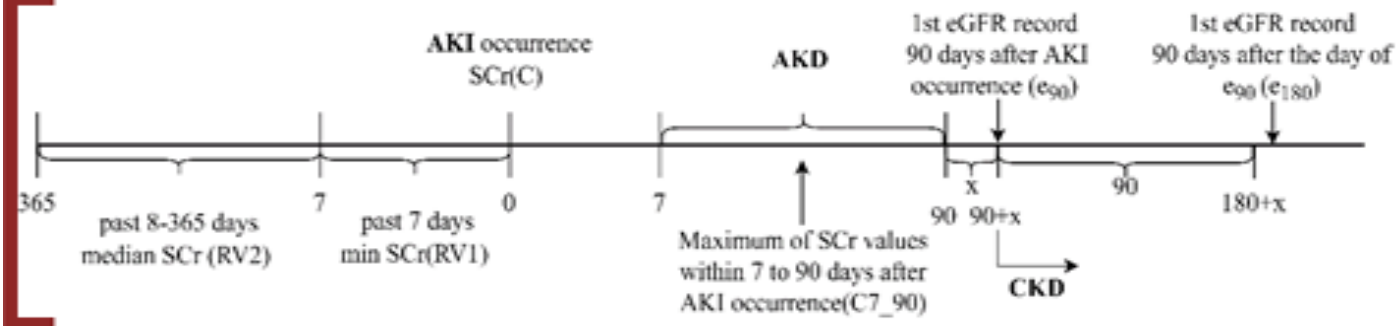
全方位腎力精準數位醫療系統



Sample preprocessing and labeling of AKI, AKD, and CKD



Timeline of AKI, AKD, and CKD labeling

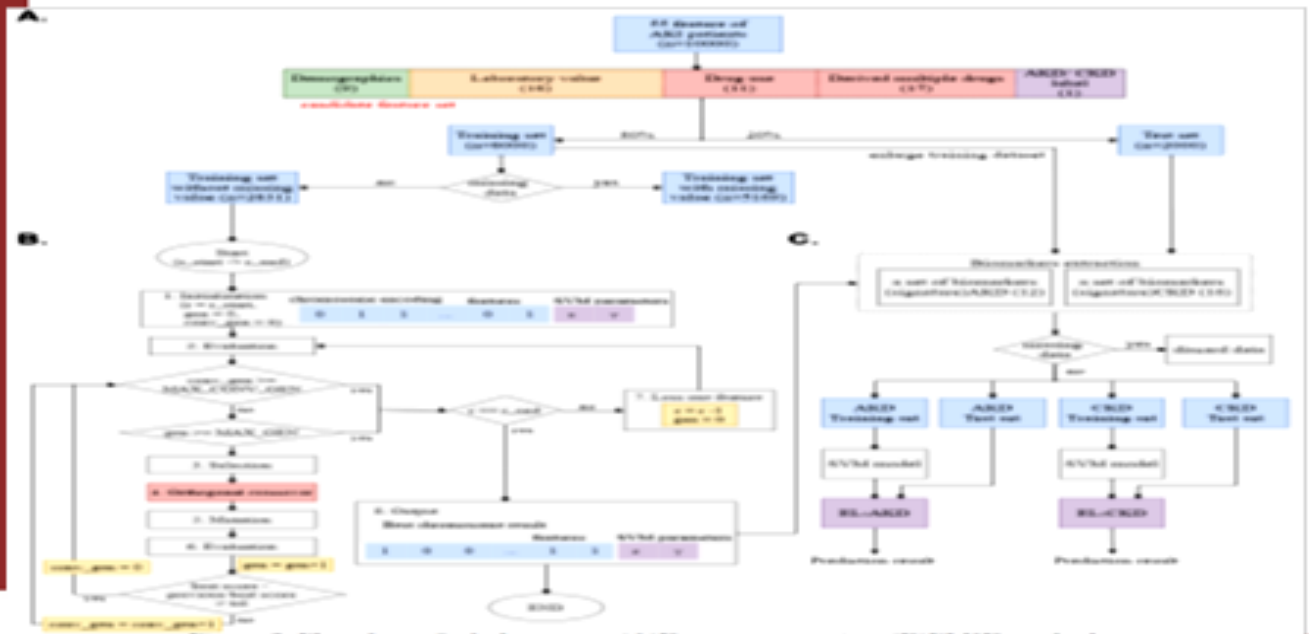


Features selection from 28 parameters of 10000 AKI samples of 2017-2020 cohort

		KDIGO AKI stage			
Characteristics	All, n=10000	Stage1, n=6324	Stage2, n=1296	Stage3, n=2380	p-value
Demographics					
Age, yr, median (IQR)	70 (60-80)	70 (60-80)	71 (60-82)	68 (59-79)	0.002
Men, n (%)	5265 (53)	3312 (52)	650 (50)	1303 (56)	0.005
Blood type, n (%)					
A	2195 (22)	1384 (22)	264 (20)	547 (23)	0.09
B	2021 (20)	1172 (19)	265 (20)	584 (25)	0.005
AB	465 (5)	284 (4)	60 (5)	121 (5)	0.98
O	3650 (37)	2249 (36)	465 (36)	936 (39)	0.56
Drug allergy, n (%)	7554 (76)	4736 (75)	981 (76)	1837 (77)	0.08
Critical illness, n (%)	6651 (67)	4122 (65)	866 (67)	1663 (70)	0.18
Laboratory values, median (IQR)					
Creatinine, mg/dl	2.1 (1.4-4.0)	1.6 (1.2-2.4)	2.1 (1.6-2.7)	6.8 (4.8-9.7)	<0.001
BUN, mg/dl	41 (24-69)	31 (20-49)	38 (24-57)	76 (55-102)	<0.001
eGFR, ml/min per 1.73m²	29.2 (15.2-47.8)	39.6 (25.0-56.7)	29.7 (21.7-40.6)	7.5 (5.1-11.4)	<0.001
Na, mmol/L	137 (133-140)	137 (134-140)	136 (132-140)	136 (133-139)	<0.001
K, mmol/L	4.1 (3.6-4.6)	4 (3.5-4.5)	4.1 (3.5-4.7)	4.5 (3.7-5)	<0.001
GPT, IU/L	21 (15-35)	22 (15-35)	25 (16-45)	17 (13-27)	0.009
GOT, IU/L	26 (21-44)	29 (21-45)	31 (23-52)	24 (18-37)	0.415
WBC differential count					
Neutrophil, %	0.75 (0.65-0.86)	0.77 (0.67-0.86)	0.79 (0.70-0.87)	0.75 (0.69-0.85)	<0.001
Lymphocyte, %	0.11 (0.06-0.19)	0.12 (0.06-0.20)	0.10 (0.05-0.17)	0.11 (0.06-0.17)	<0.001
Monocyte, %	0.07 (0.05-0.10)	0.07 (0.05-0.10)	0.07 (0.042-0.094)	0.07 (0.05-0.10)	0.144
Eosinophil, %	0.01 (0.00-0.02)	0.01 (0.00-0.02)	0.005 (0-0.012)	0.01 (0.001-0.05)	<0.001
Basophil, %	0.005(0.001-0.008)	0.005(0.001-0.008)	0.005 (0.00-0.005)	0.004(0.001-0.007)	<0.001
Medication use, n (%)					
ACEi/ARB	1196 (12)	851 (13)	142 (11)	225 (9)	<0.001
Antibiotics	4526 (45)	2986 (47)	668 (52)	874 (37)	<0.001
Anticholinergic drug	462 (5)	295 (5)	64 (5)	100 (4)	0.348
Antifungal drug	141 (1)	94 (1)	22 (2)	25 (1)	0.055
Antihypertensive drug	1745 (17)	1056 (17)	181 (14)	508 (21)	<0.001
Antiviral drug	77 (1)	49 (1)	17 (1)	11 (0)	0.023
Chemotherapy	371 (4)	285 (5)	50 (4)	36 (2)	<0.001
Diuretics	2445 (24)	1627 (26)	305 (24)	513 (21)	<0.001
SGLT2i	52 (1)	45 (1)	6 (0)	1 (0)	0.004
NSAID	595 (4)	275 (4)	75 (6)	45 (2)	<0.001
PPI	2291 (23)	1526 (24)	304 (23)	461 (19)	<0.001

IQR, interquartile range; BUN, blood urea nitrogen; GPT, glutamic pyruvic transaminase; GOT, glutamic oxaloacetic transaminase; WBC, white blood cell; ACEi, angiotensin converting enzyme inhibitor; SGLT2i, sodium glucose cotransporters 2 inhibitors; NSAID, non-steroidal anti-inflammatory; PPI, proton pump inhibitor; KDIGO, Kidney Disease Improving Global Outcomes.

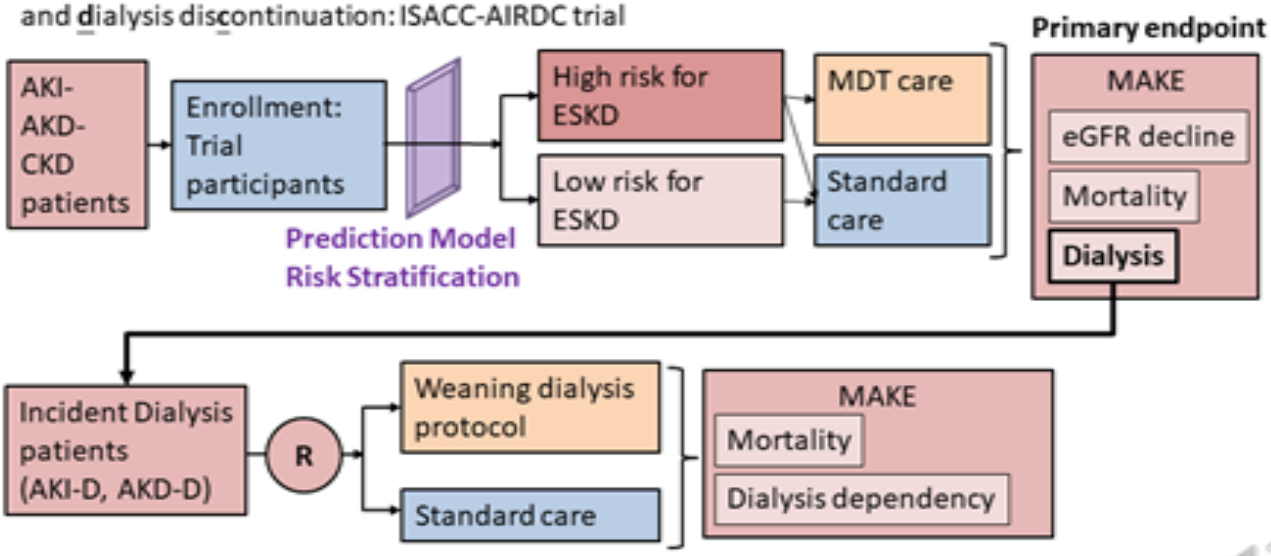
Machine learning-based prediction model to find out "most-in-need" AKI patients



(Unpublished data)

Prediction model-assisted risk stratification of AKI patients

Intensified AKD care to reduce CKD with AI prediction model-based risk stratification and dialysis discontinuation: ISACC-AIRDC trial



Features of EL-AKD and EL-CKD

Rank	EL-AKD (12 features)	MED	p-value	EL-CKD (15 features)	MED	p-value
1	AKI stage	0.03	< 0.001	eGFR	0.13	< 0.001
2	Diuretics	0.02	< 0.001	Creatinine	0.10	< 0.001
3	eGFR	0.01	0.22	GOT	0.01	0.43
4	NSAID (injection)	0.01	0.08	Diuretics (injection)	0.01	< 0.001
5	Anti-cholinergic	0.01	0.10	NSAID	0.01	0.100
6	ACEI	0.008	0.06	Monocyte	0.009	< 0.001
7	PPI (oral)	0.007	0.05	Blood type A	0.007	0.98
8	Creatinine	0.006	0.32	Diuretics	0.004	< 0.001
9	BUN	0.004	0.22	SGLT2i	0.004	0.68
10	Antibiotics	0.002	0.07	Antibiotics & Chemotherapy & NSAID (injection)	0.003	0.18
11	GPT	0.001	0.58	Antibiotics (oral)	0.003	0.01
12	Drug allergy	< 0.001	0.43	Drug allergy	< 0.001	0.001
13				Anti-fungal	< 0.001	0.68
14				Basophil	< 0.001	< 0.001
15				AKI stage	< 0.001	< 0.001

Performance comparison of EL-AKD and EL-CKD with other machine learning models.

Model	Features	AKD			Model	Features	CKD		
		ACC (%)	MCC	AUC			ACC (%)	MCC	AUC
EL-AKD	12	70.37	0.397	0.747	EL-CKD	15	83.20	0.664	0.906
ELAKI-LR	12	66.23	0.323	0.700	ELAKI-LR	15	83.98	0.680	0.912
Pv-SVM	12	65.14	0.301	0.679	Pv-SVM	15	81.25	0.627	0.810
Pv-J48	12	61.87	0.240	0.602	Pv-J48	15	78.52	0.597	0.790
Pv-LR	12	65.36	0.306	0.693	Pv-LR	15	83.20	0.668	0.919
Pv-Adaboost	12	63.94	0.265	0.686	Pv- Adaboost	15	79.88	0.600	0.885

Compare ELAKI with models using p-value to select the same number of top-ranked features with the methods SVM, J48 decision tree, logistic regression, and adaptive boosting. ACC, accuracy; MCC, Matthews correlation coefficient; AUC, area under the receiver operating characteristic curve; LR, logistic regression; SVM, support vector machine. Adaboost, adaptive boosting.

Molecular signature of renal progression in septic AKI: a multi-omic approach

Table 1. Patient demographic data.

Characteristics	N	%
Microorganism		
GPC	19	15.40%
GNB	79	64.20%
Other	25	20.30%
Gender		
Male	69	56.10%
Female	54	43.90%
Age (Mean year)	65.81	
AKI		
Stage 1	34	27.60%
Stage 2	12	9.80%
Stage 3	7	5.70%
Stage 0	70	56.90%
CKD		
1	20	16.30%
0	103	83.70%
qSOFA (Day 1)		
0	82	67.20%
1	34	27.90%
2	6	4.90%
qSOFA (Day 7)		
0	48	64.90%
1	19	25.70%
2	7	9.50%

Abbreviation: GPC: Gram-positive coccus; GNB: Gram-Negative Bacteria; CKD: chronic kidney disease; qSOFA: quick sepsis related organ failure assessment

Features:

1. Clinicalparameters
2. Lipidomic metabolite
3. Immune markers

↓

Machine learning algorithm to integrate big datasets

↓

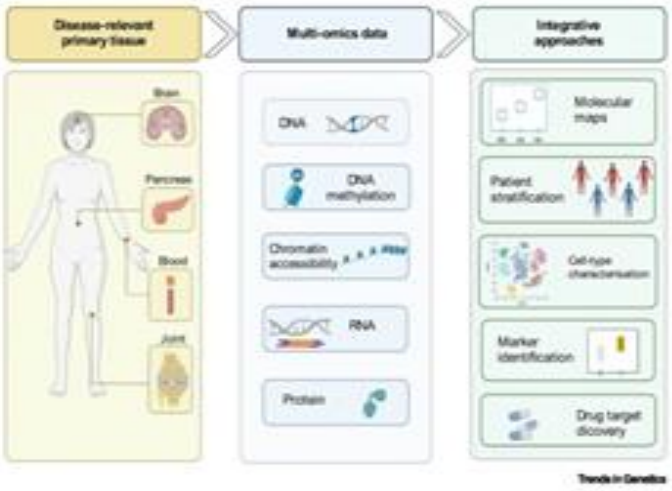
Biological network / Organ cross-talk

多組學 Multi-omics

- 整合兩個或多個組學資訊，以明確某種生理機制。
- 為生理機制提供更多證據，進而更深入瞭解生理病理中複雜的分子調控與因果關係。

Multiomics strategy

- *Genomics*
- *Epigenomics*
- *Transcriptomics*
- *Proteomics*
- *Metabolomics*
- *Microbiomics*



Target metabolomics: lipophilic metabolite

MxP® Quant 500 XL OR Biocrates P180

1,400+ biomarker candidates = 1,000+ metabolites & 400+ metabolite sums and ratios

107 small molecules (14 classes)

- Alkaloids (1)
- Amine oxides (1)
- Amino acids (20)
- Amino acid related (20)
- Bile acids (14)
- Biogenic amines (9)
- Carbohydrates and related (1)
- Carboxylic acids (7)
- Cresols (1)
- Fatty acids (12)
- Hormones and related (4)
- Indoles and derivatives (4)
- Nucleobases and related (2)
- Vitamins and cofactors (1)

912 lipids (25 classes)

- Acylcarnitines (40)
- Phosphatidylcholines (80)
- Lysophosphatidylcholines (10)
- Sphingomyelins (15)
- Cholesteryl esters (22)
- Ceramides (29)
- Dihydroceramides (8)
- Hexosylceramides (19)
- Dihexosylceramides (6)
- Trihexosylceramides (6)
- Diglycerides (44)
- Triglycerides (242)
- Phosphatidic acids (41)
- Lysophosphatidic acids (8)
- Phosphatidylethanolamines (93)
- Lysophosphatidylethanolamines (43)
- Phosphatidylglycerols (64)
- Lysophosphatidylglycerols (10)
- Phosphatidylinositols (32)
- Lysophosphatidylinositols (16)
- Phosphatidylserines (18)
- Lysophosphatidylserines (12)
- Sphinganines and sphingosines (8)
- Sphinganine and sphingosine phosphates (8)
- Monoacylglycerols (12)

NEW

400+ metabolite sums and ratios – MetabolNDICATOR™

AKI-AKD-CKD continuum:

Unmet clinical need and market-oriented

01 應用人工智慧系統提供精準醫療

自動診斷 → 偵測定位 → 即時介入

提升個案管理效能、提升醫療品質

02 資料庫建立與整合

流行病學 / 基因表現 / 免疫指標 / 病理影像 / 病人作習 / 環境暴露史

剖析台灣國民基因及環境因素與腎臟病關聯

03 發展AI預測模型

AKI-AKD-CKD 連程平台AI預測模型

嵌入臨床決策支持系統

早期預測、早期預防

04 開發生物標記與治療標的

拓展新治療領域