Acute pancreatitis

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West China Biobanks

Integrated Traditional Chinese and Western Medicine

West China Hospital of Sichuan University

PancreasFest 2019 · Pittsburgh

Management – Practice Guidelines

Author (country)	Journal (year)	Severity prediction (within 48 hrs)	Pancreatic necrosis	Fluid therapy	Infected pancreatic necrosis (timing and methods)	Tertiary referral
Chinese Society of Surgery and Association of Integrative Medicine	*Chinese Crit Care Med (2007)*	APACHE II ≥ 8 Ranson ≥ 3 Balthazar CT score ≥ II	CECT, NA	NA	Time (NA); open mainly	NA
IAP and AGA	*Pancreatol (2013)*	SIRS	CECT, 3-4 d, for predicted severe cases	Optimal	> 4 wk; percutaneous drainage > minimally invasive > open; surgery, imaging and endoscopy etc.	Surgery, endoscopy
ACG	*Am J Gastroenterol (2013)*	BISAP	CECT or MRI, 2-3 d	Aggressive	> 4 wk; percutaneous drainage > minimally invasive > open; surgery, imaging and endoscopy etc.	NA
Japanese Pancreatic Society	*J Hepatobiliary Pancreat Sci (2015)*	JSS	CECT or MRI, < 1 wk	Aggressive	> 4 wk; percutaneous drainage > minimally invasive > open; surgery, imaging and endoscopy etc.	Severe
Italian Pancreatology Association	*Dig and Liver Dis (2016)*	NA	CECT or MRI, < 3 d	Aggressive	> 4 wk; percutaneous drainage > minimally invasive > open; surgery, imaging and endoscopy etc.	NA
AGA	*Gastroenterol (2018)*	NA	NA	Goal-directed	NA	NA
National Institute for Health and Care Excellence (NICE)	*BMJ (2018)*	NA	NA	NA	Endoscopic drainage, if anatomically feasible	Necrotic, infective, haemorrhagic, or systemic complications
World Society of Emergency Surgery (WSES)	*World J Emerg Surg (2019)*	CRP ≥ 150 mg/l BISAP	CECT 72–96 h, for predicted severe cases	Goal-directed	> 4 wk; percutaneous drainage > minimally invasive > open; surgery, imaging and endoscopy etc.	NA

AGA recommendations

Recommendation	Strength of recommendation	Quality of evidence
1A. In patients with AP, the AGA suggests using goal-directed therapy for fluid management. *Comment: The AGA makes no recommendation whether normal saline or Ringer's lactate is used.*	Conditional	Very low
1B. In patients with AP, the AGA suggests against the use of HES fluids. Conditional Very low.	Conditional	Very low
2. In patients with predicted severe AP and necrotizing AP, the AGA suggests against the use of prophylactic antibiotics.	Conditional	Low
3. In patients with acute biliary pancreatitis and no cholangitis, the AGA suggests against the routine use of urgent ERCP.	Conditional	Low
4. In patients with AP, the AGA recommends early (within 24 h) oral feeding as tolerated, rather than keeping the patient nil per os.	Strong	Moderate
5. In patients with AP and inability to feed orally, the AGA recommends enteral rather than parenteral nutrition.	Strong	Moderate
6. In patients with predicted severe or necrotizing pancreatitis requiring enteral tube feeding, the AGA suggest either NG or NJ route.	Conditional	Low
7. In patients with acute biliary pancreatitis, the AGA recommends cholecystectomy during the initial admission rather than after discharge.	Strong	Moderate
8. In patients with acute alcoholic pancreatitis, the AGA recommends brief alcohol intervention during admission	Strong	Moderate

Crockett et al. Gastroenterol 2018

Unmet need in managment

- Pharmacological therapies (for acinar cells?)
- Multiple disciplinary team & hierarchical (multi-level hospitals)
- Disease severity classification and early prediction
- Fluid therapy: Type of fluid? Rate of given? Judge fluid responsiveness?
- Specific and early organ support therapy
- Treatment of aetiology (e.g. biliary, alcohol and genetics) and co-morbidities (e.g. diabetes, fatty liver, hypertriglyceridaemia)
- Local complications (timing and methods)

Project 1 – Preclinical validation and RCTs for pathological calcium signalling inhibitors

Project 1 – Research basis

- **Pathological calcium signalling proposed:**

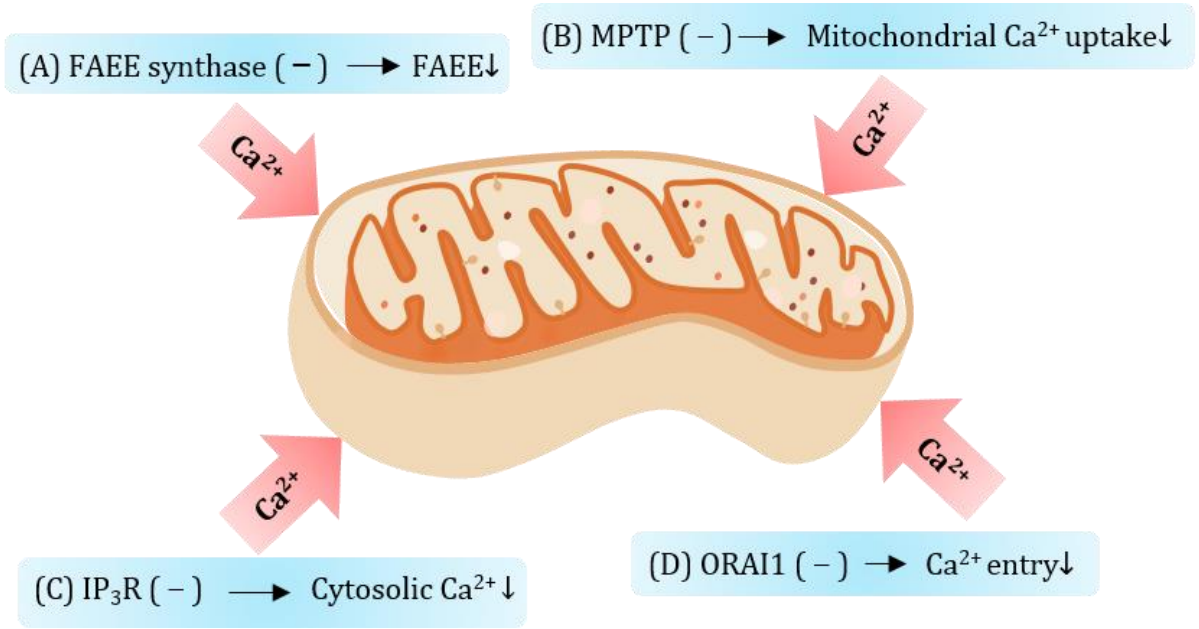
Ward JB et al. Lancet 1995;346:1016-9

- **Hypothesis first tested in experimental acute pancreatitis:**

Ward JB et al. Gastroenterol 1996;111:481-91

Ole H. Petersen

Robert Sutton



Liverpool, UCLA and Chengdu:

- **CEL inhibitor, 3-benzyl-6-chloro-2-pyrone (3-BCP)**

Huang W and Booth D et al. Gut 2014;63:1313–1324

- **ORAI1 inhibitor, GSK-7975A and CM_128**

Wen L and Voronina S et al. Gastroenterol 2015;149:481-92.e7

- **MPTP inhibitor, DEB025 and TRO40303**

Mukherjee R and Mareninova OA et al. Gut 2016;65:1333-46

- **IP_3R inhibitor, caffeine**

Huang W and Cane M et al. Gut 2017;66:301-313

Other groups:

- **SOCE inhibitor pyrtriazoles**

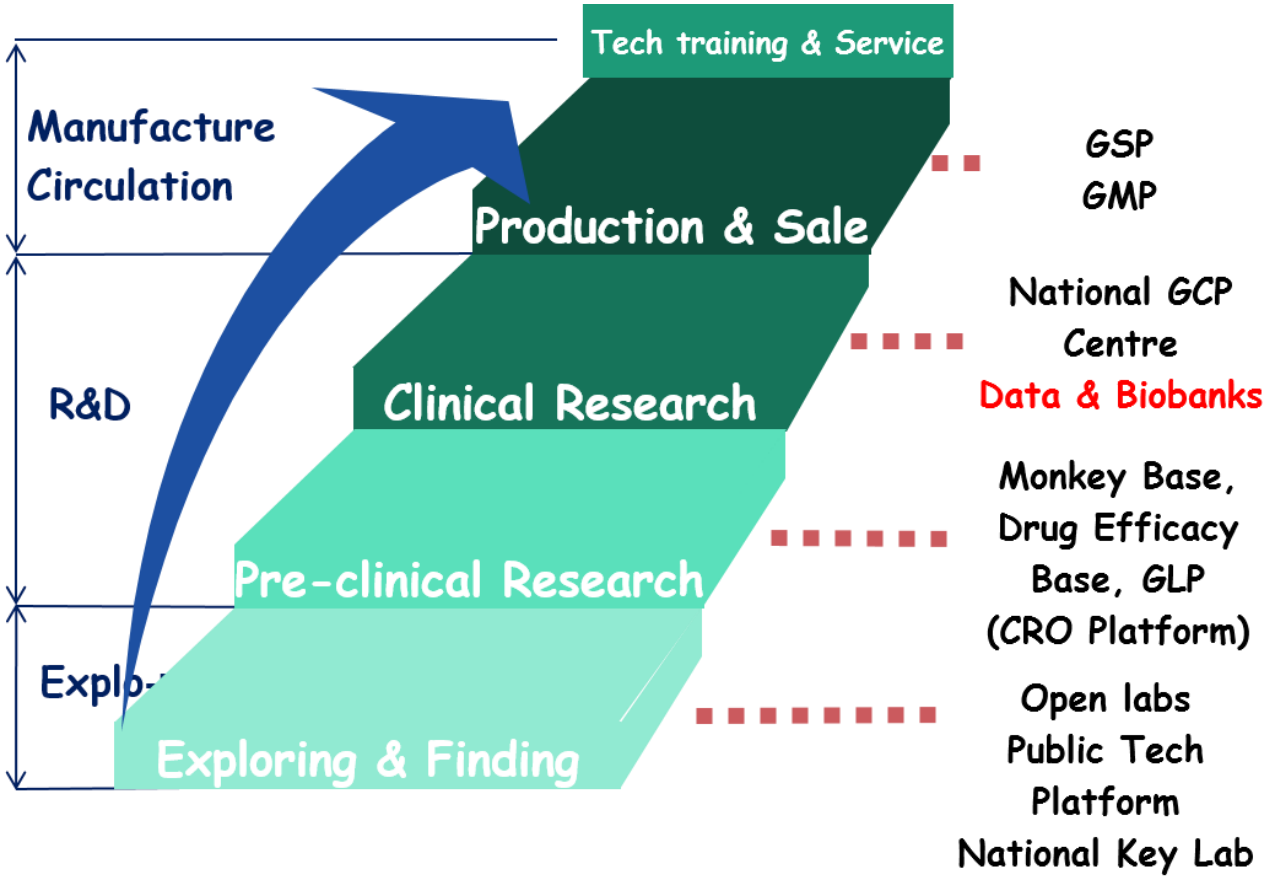
Riva B et al. J Med Chem 2018;61:9756-9783

- **ORAI1 inhibitor, CM4620**

Waldron RT et al. J Physiol 2019;597:3085-3105

Project 1 – Proposed work

West China Drug Discovery Chain



CalciMedica

Michael Dunn
President

Ken Stauderman
CSO

Sudarshan Hebbar
CMO

Cypralis Pipeline

Target to Lead	Lead Optimisation	Pre-Clinical Dev

- Liver Disease (Gilead collaboration)
- Acute Tissue Injury
- Inflammation *
- Acute Tissue Injury *

* cyclophilin subtype selective

Michael Peel CSO

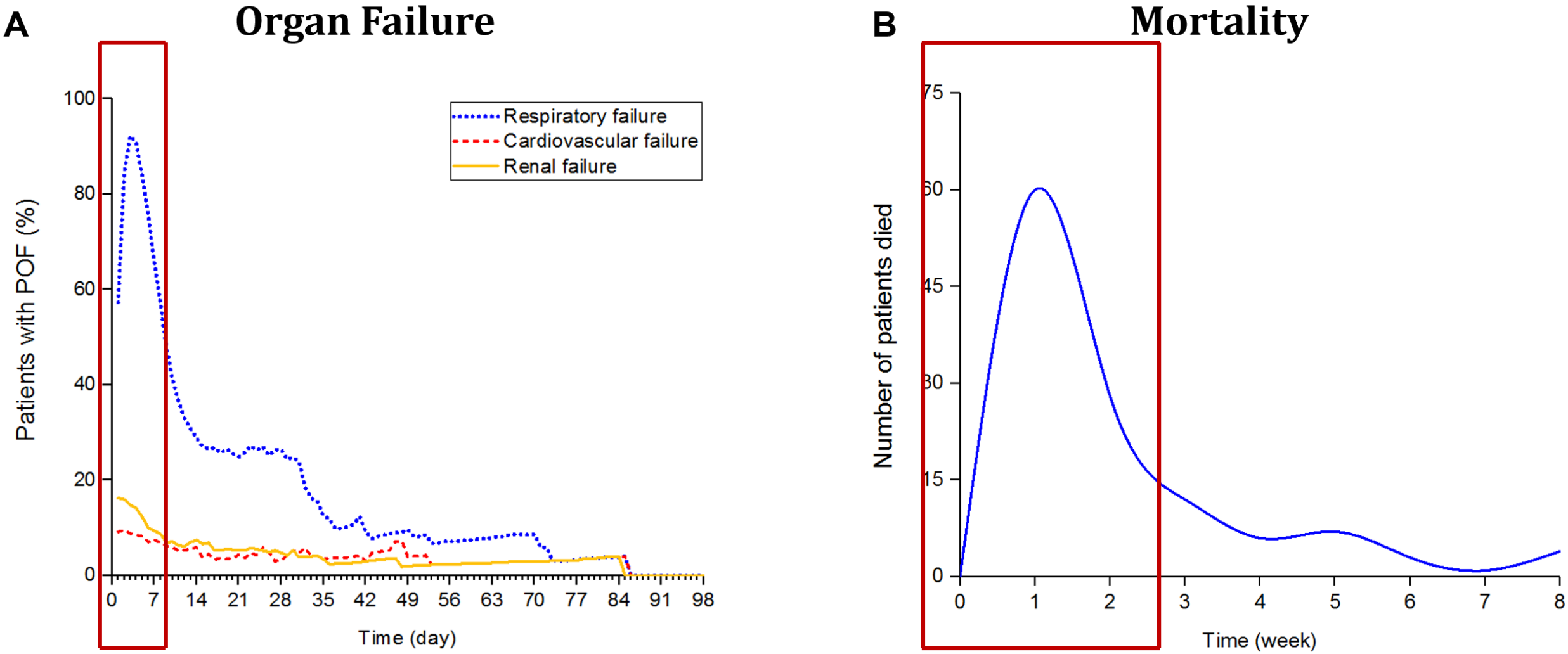
Cypralis

Farshu Ma CEO

睿诺医疗科技
FARSIGHT MEDICAL TECHNOLOGY

Project 2 – Early disease severity predictive biomarker discovery and validation

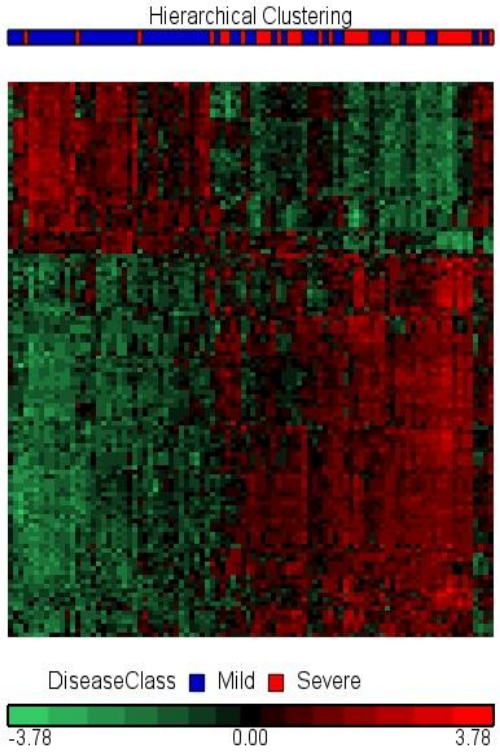
Project 2 – Research basis 1



Guo et al. Ann Surg 2014;259:1201-7; Shi N et al. Gut 2019 pii: gutjnl-2019-318241

Project 2 – Research basis 2

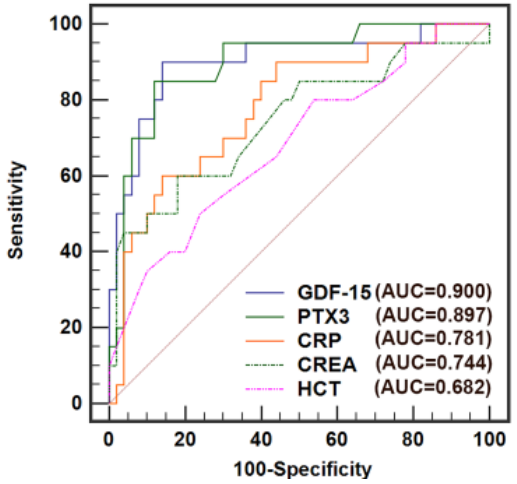
24 hrs, 92 Arrays
126 DE genes

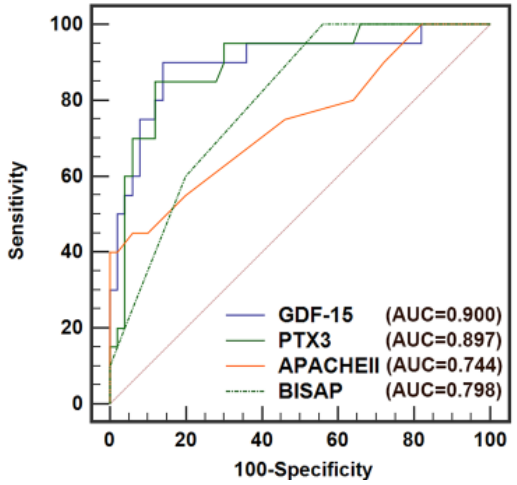


Nunes QM and Huang W et al. 2019 Manuscript ***in preparing***

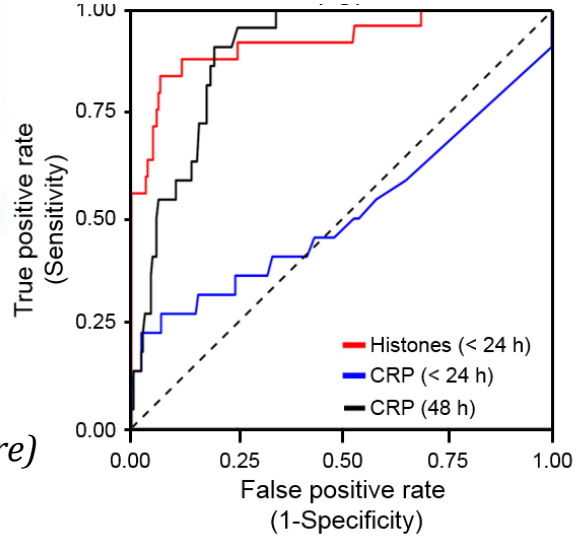
Deng L et al. Medicine (Baltimore) 2017;96:e7312

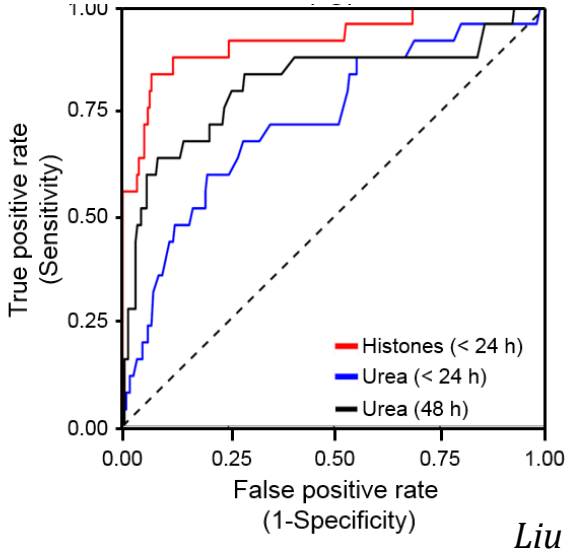
Multiplex for cytokines

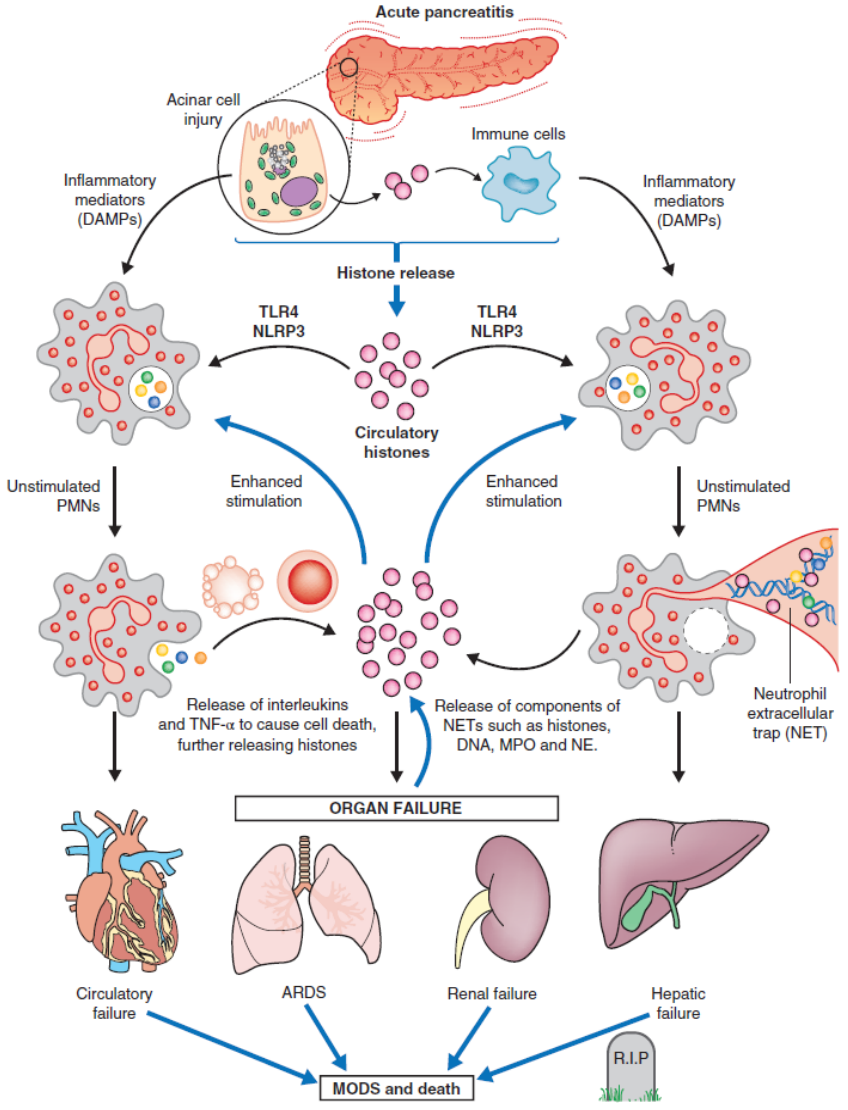




Circulating histones





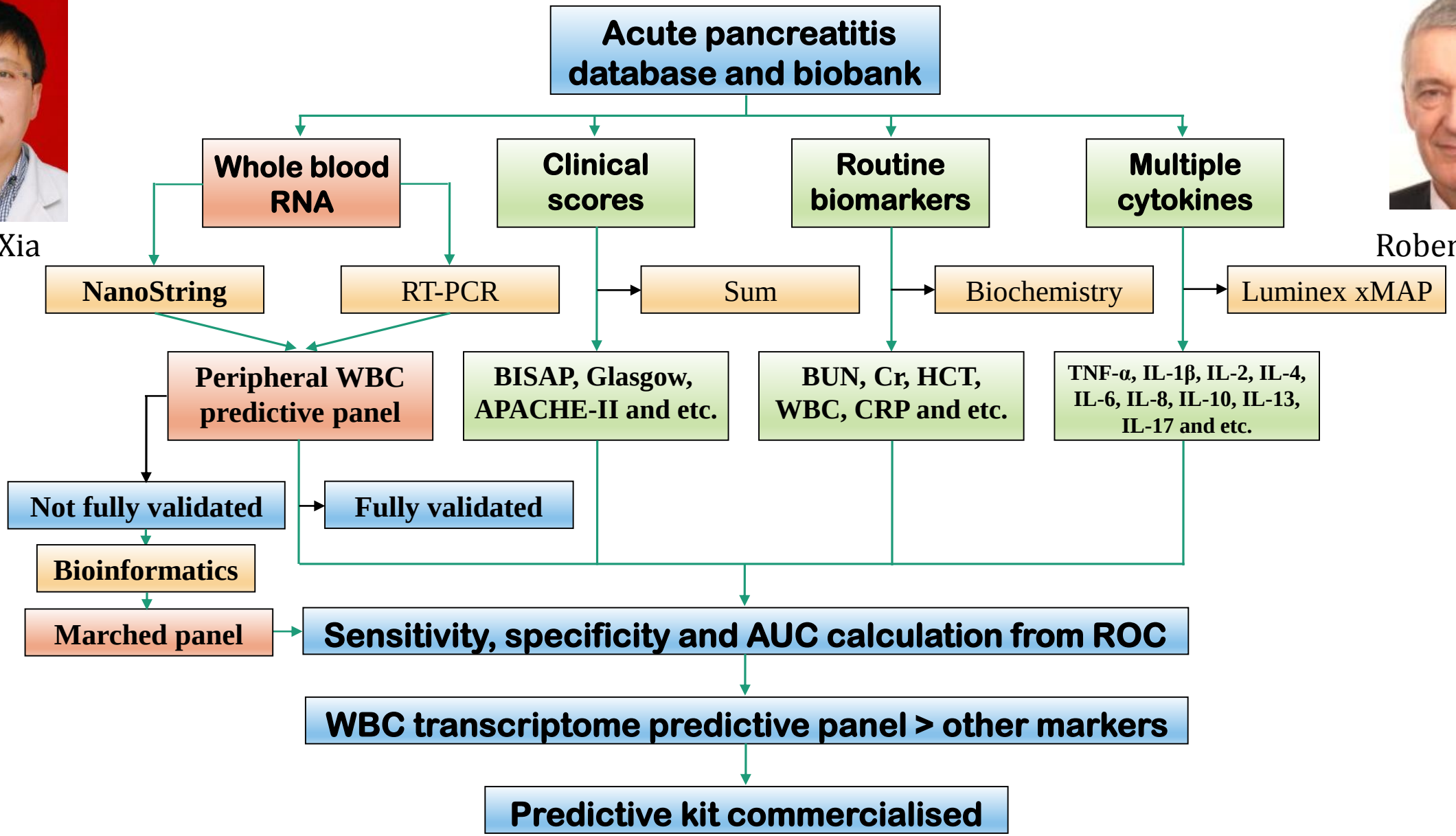


Liu T and Huang W et al. Br J Surg 2017;104(9):1215-1225

Project 2 – Proposed work

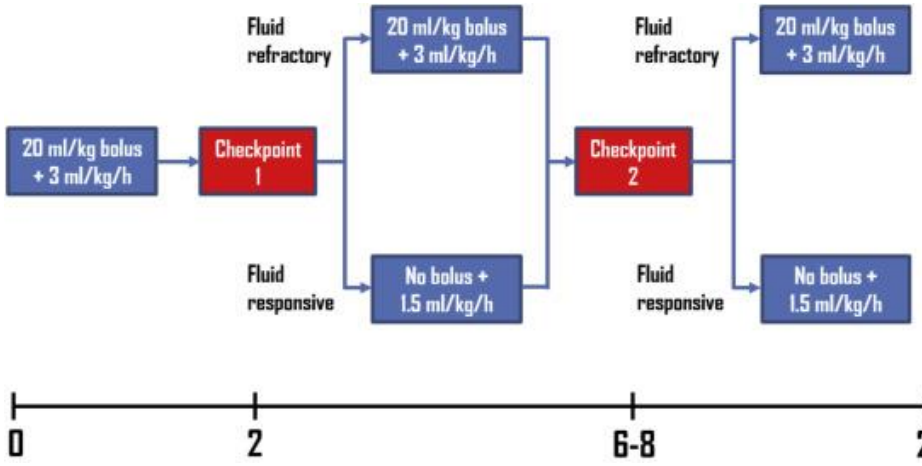
Qing Xia

Robert Sutton



Project 3 – Early fluid therapy and monitoring fluid responsiveness in acute pancreatitis

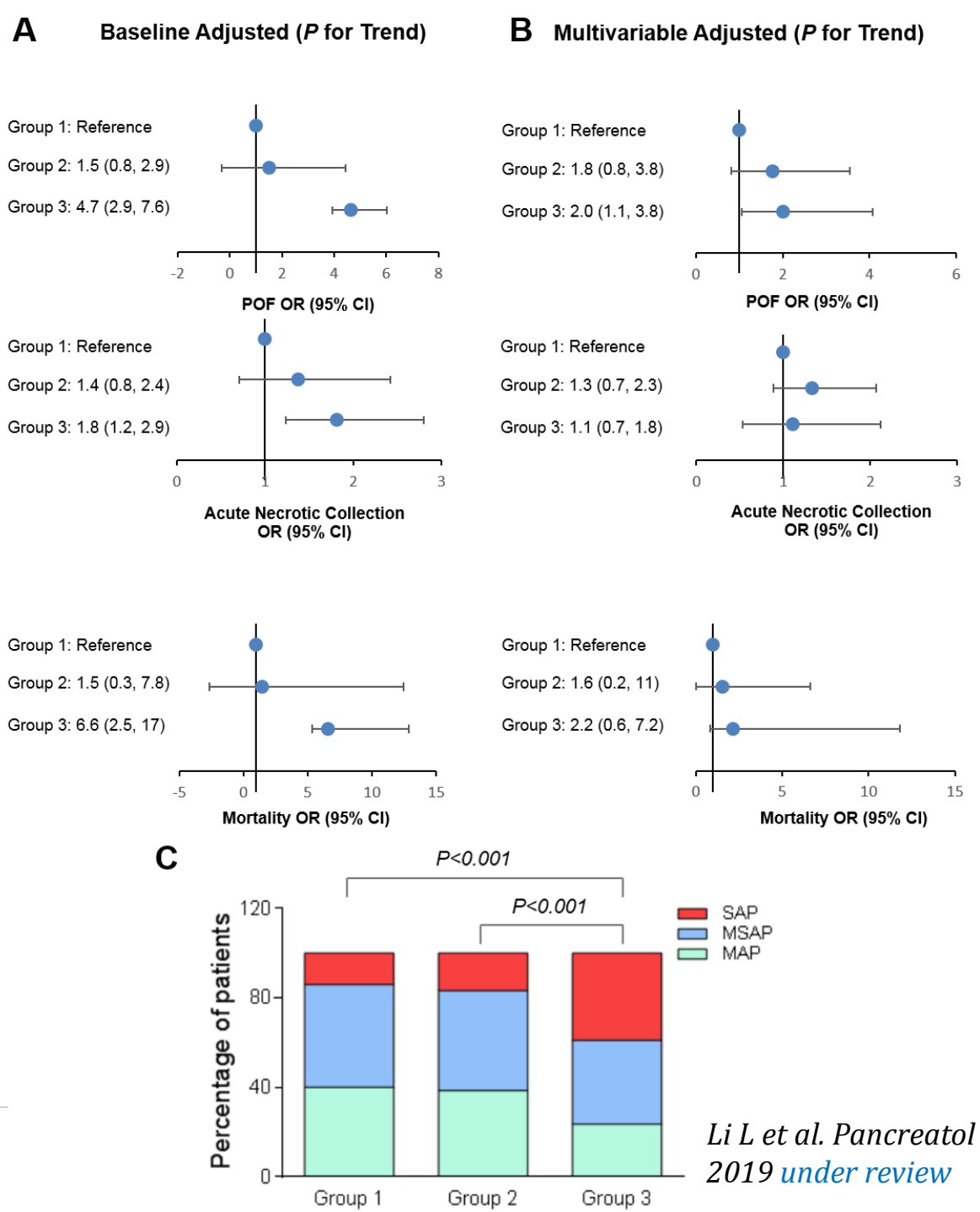
Project 3 - basis



Clinical outcomes	Group 1	Group 2	Group 3	Group 4	1 vs. 2	3 vs. 4
	Responsive at 2 h (n = 19)	Refractory at 2 h (n = 4)	Responsive at 6–8 h (n = 14)	Refractory at 6–8 h (n = 9)	*P*	*P*
Persistent organ failure	10	4	6	8	0.12	**0.04**
Pancreatic necrosis	7	4	4	7	0.07	**0.005**
Necrosectomy	6	0	1	5	0.53	**0.018**
Infected pancreatic necrosis	6	0	1	5	0.53	**0.018**
Extrapancreatic infections	4	0	1	7	1	**0.005**
Need intensive care	10	3	5	8	0.41	**0.012**
Length of hospital stay, days, median (IQR) [a]	20 (14–66)	20 (13–24)	18 (11–21)	56 (24–77)	0.65	**0.019**
Mortality	4	0	0	4	1	**0.014**

IQR, interquartile range
P value in bold indicates that there was significant different at level of 0.05 between the designated two groups.
[a] Patients died during the first two weeks of admission were excluded from the analysis

Jin T et al. HPB(Oxford) 2018; 20(11):1082-1091



Li L et al. Pancreatol 2019 under review

Project 3 - Passive leg raising test

JAMA | The Rational Clinical Examination

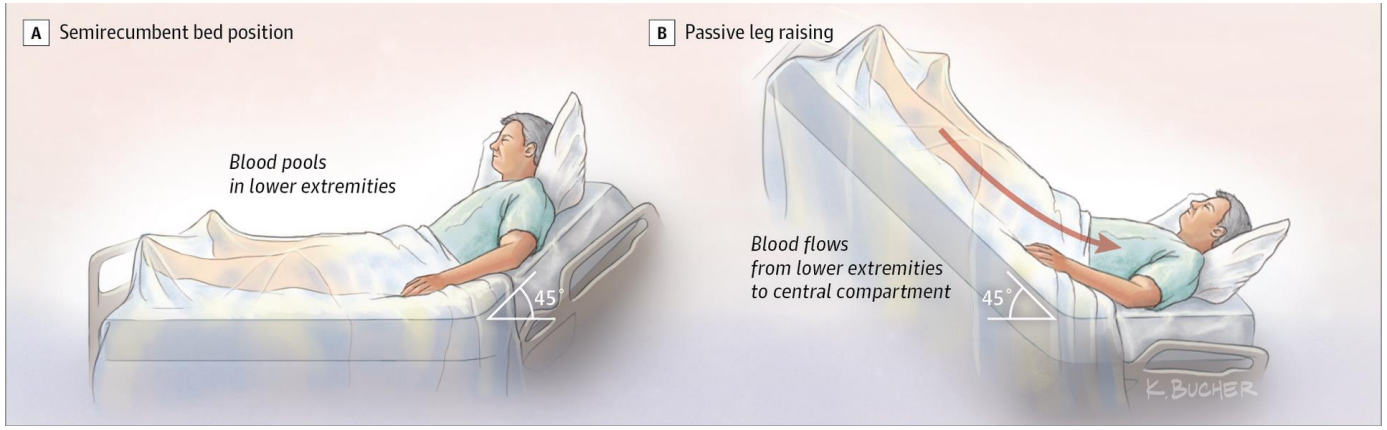
Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids?

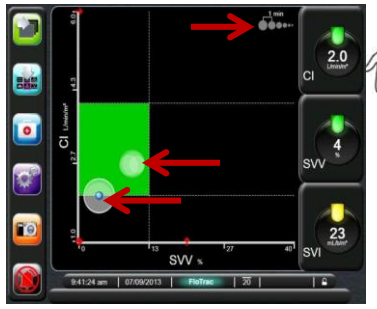
Table. Summary of Diagnostic Accuracy for Hypovolemia Responsive to Fluids[a]

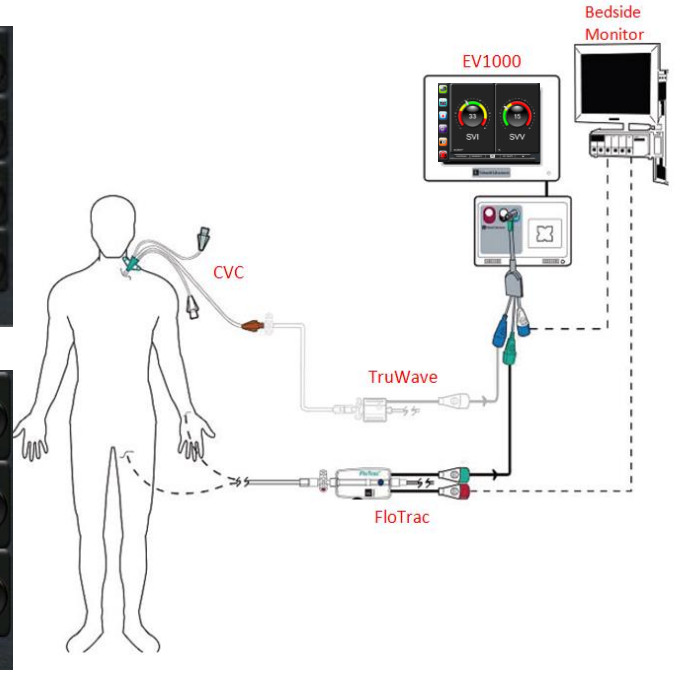
Measures and Included Studies	No. of Studies	No. of Patients	Cutoff for Measures, Mean (Range)[b]	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR (95% CI)	I^2, %	Negative LR (95% CI)	I^2, %	Diagnostic OR (95% CI)
Static Measure										
Central venous pressure[44,47,49,71-74]	7	356	8 mm Hg (6-9)	62 (54-69)	76 (60-87)	2.6 (1.4-4.6)	0	0.50 (0.39-0.65)	58	5 (2-11)
Dynamic Measures										
Pulse pressure variation										
Controlled ventilation, V_t≥7.0 mL/kg[36,37,40,66,75-83,92,96,97]	17	768	11 (4-15)[c]	84 (75-90)	84 (77-90)	5.3 (3.5-8.1)	52	0.19 (0.12-0.30)	50	28 (13-57)
Controlled ventilation, V_t<7.0 mL/kg[37,84-87]	5	219	8 (5-12)[c]	72 (61-81)	91 (83-95)	7.9 (4.1-16)	22	0.30 (0.21-0.44)	0	26 (11-61)
Stroke volume variation										
Controlled ventilation[34,36,77,78,80,81,88-90]	9	343	13 (10-20)	79 (67-87)	84 (74-90)	4.9 (2.8-8.5)	45	0.25 (0.15-0.43)	20	19 (7-53)
Spontaneous breathing[48,49]	2	53	10-12[d]	57-100[d]	44-57[d]	1.0-2.3[d,e]		0.05-0.98[d,e]		1-43[d]
Inferior vena cava variation										
Controlled ventilation[28,50,51,90]	4	137	15 (12-21)	77 (44-94)	85 (49-97)	5.3 (1.1-27)	76	0.27 (0.08-0.87)	71	20 (2-222)
Spontaneous breathing[52,53]	2	99	40-42[d]	31-70[d]	80-97[d]	3.5-9.3[d]		0.38-0.71[d]		9-13[d]
Response to passive leg raising										
Change in cardiac output[24,35,38,39,41,43,45,48,53,60,91-97]	17	788	11 (7-15)	88 (80-93)	92 (89-95)	11 (7.6-17)	60	0.13 (0.07-0.22)	0	88 (39-199)
Change in pulse pressure[24,38,41,43,48]	5	278	10 (9-12)	62 (54-70)	83 (76-88)	3.6 (2.5-5.4)	0	0.45 (0.36-0.57)	0	8 (5-14)
Change in cardiac output following passive leg raising										
Controlled ventilation[38,41,92,93,96,97]	6	294	10 (7-12)	92 (82-97)	92 (86-96)	11 (6.3-21)	41	0.08 (0.03-0.21)	0	139 (41-474)
Spontaneous breathing[35,39,43,53,94]	5	181	12 (10-13)	88 (80-94)	88 (80-94)	7.0 (3.8-13.1)	60	0.22 (0.09-0.54)	0	54 (15-195)

Bentzer P et al. JAMA 2016;316:1298-309

Project 3 – Proposed work

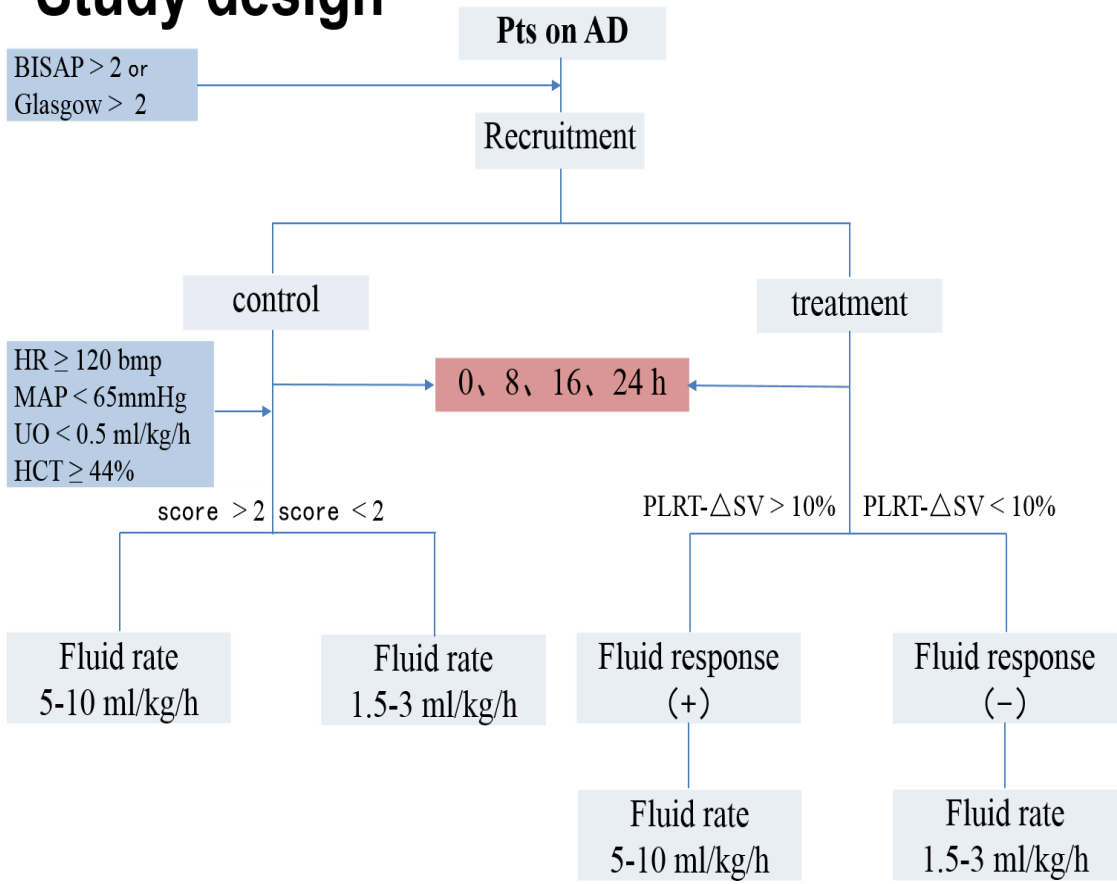






China-NZ Governmental Strategic Alliance Award

Study design



Jin T et al. 2019 Manuscript ***in preparing***

Project 4 – Omics studies with acute pancreatitis

Project 4 – Research resources

Capacity: 10 M
Stored: 2 M

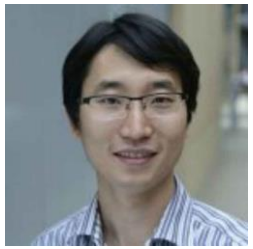
Healthy volunteers: 300,000 with serum, plasma and buffy coat: 800,000

Tumour and match blood: 200,000

Hepatitis B: 390,000

Western China geriatric cohort: 80,000

Others: 600,000

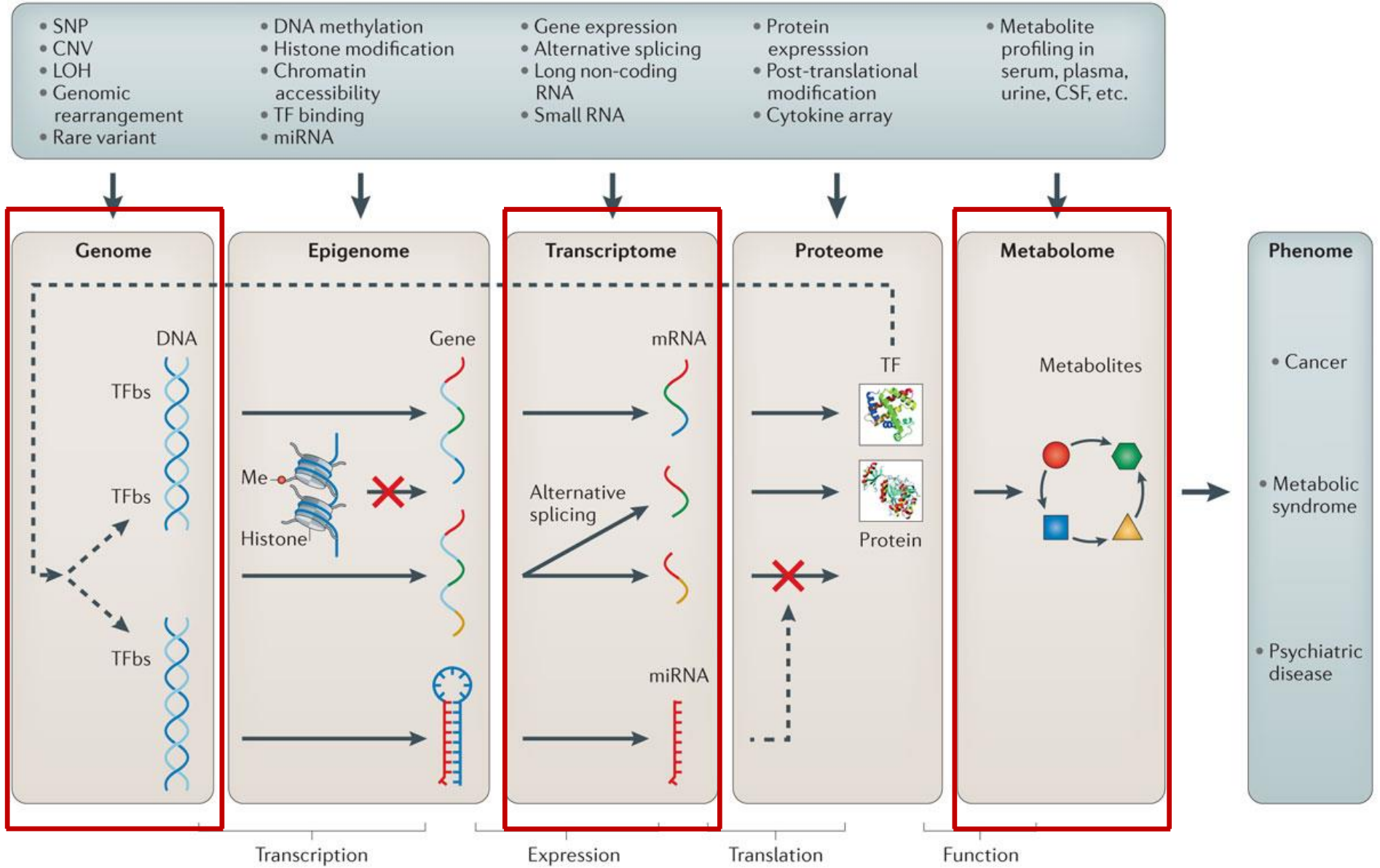


Sate Key Laboratory of Biotherapy:

Professor of genetics and bioinformatics

Nature, Cell, Science, Nat Genet, Nat Commun, Mol Biol Evo, Genome Biol

Project 4 – Proposed work



Ritchie MD et al. Nat Rev Genet 2015;16:85-97

Acknowledgments

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- State Key Laboratory of Biotherapy of Sichuan University: Professors Lu Chen and Xianghui Fu; colleagues from Nanjing, Nanchang and Shanghai
- International collaborators: Professors Robert Sutton (Liverpool), John A. Windsor (Auckland), Vikesh K. Singh (Baltimore), J Enrique Dominguez-Munoz (Santiago de Compostela)
- Invitation from Professor David C. Whitcomb (Pittsburgh) and PancreasFest

- Email address: dr_wei_huang@scu.edn.cn; wetchat: iPancreas

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