

Odrzucanie przeszczepu narządowego

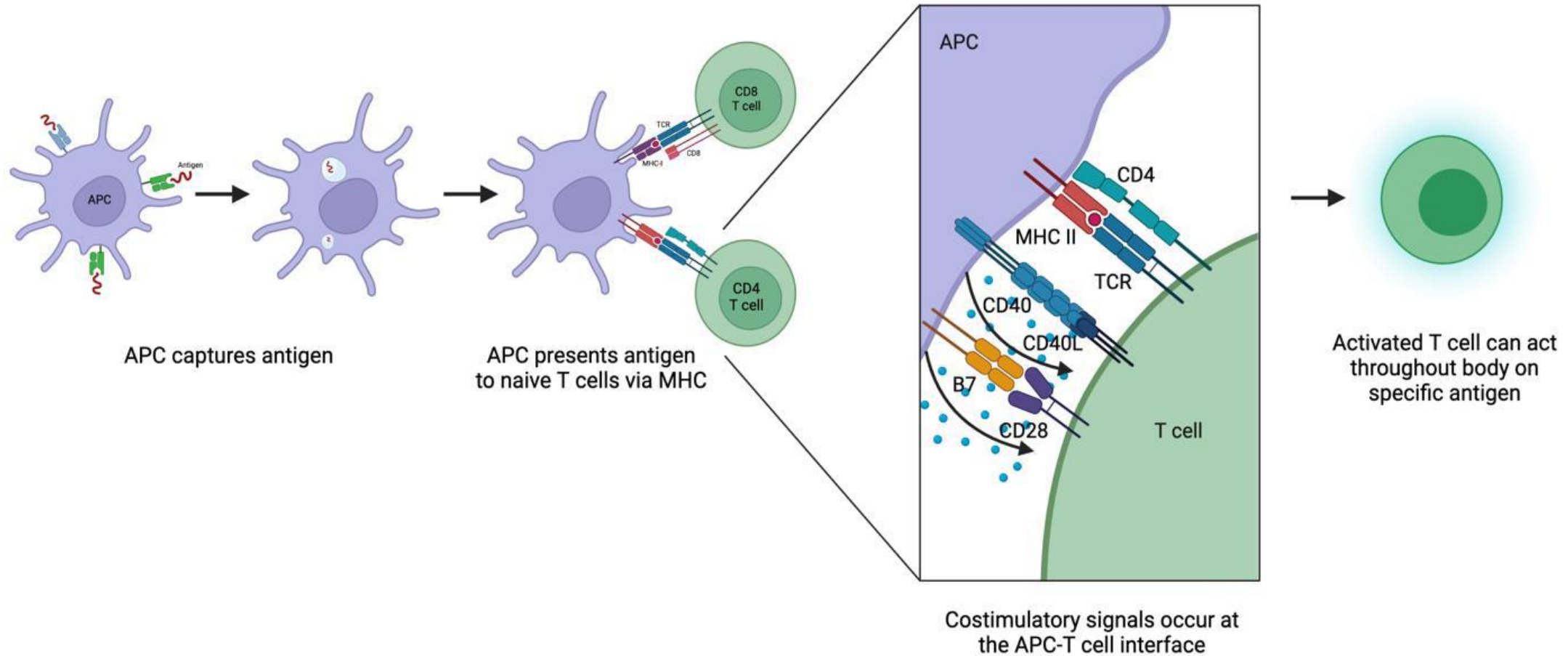
Bartosz Foronczewicz

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Warszawski Uniwersytet Medyczny

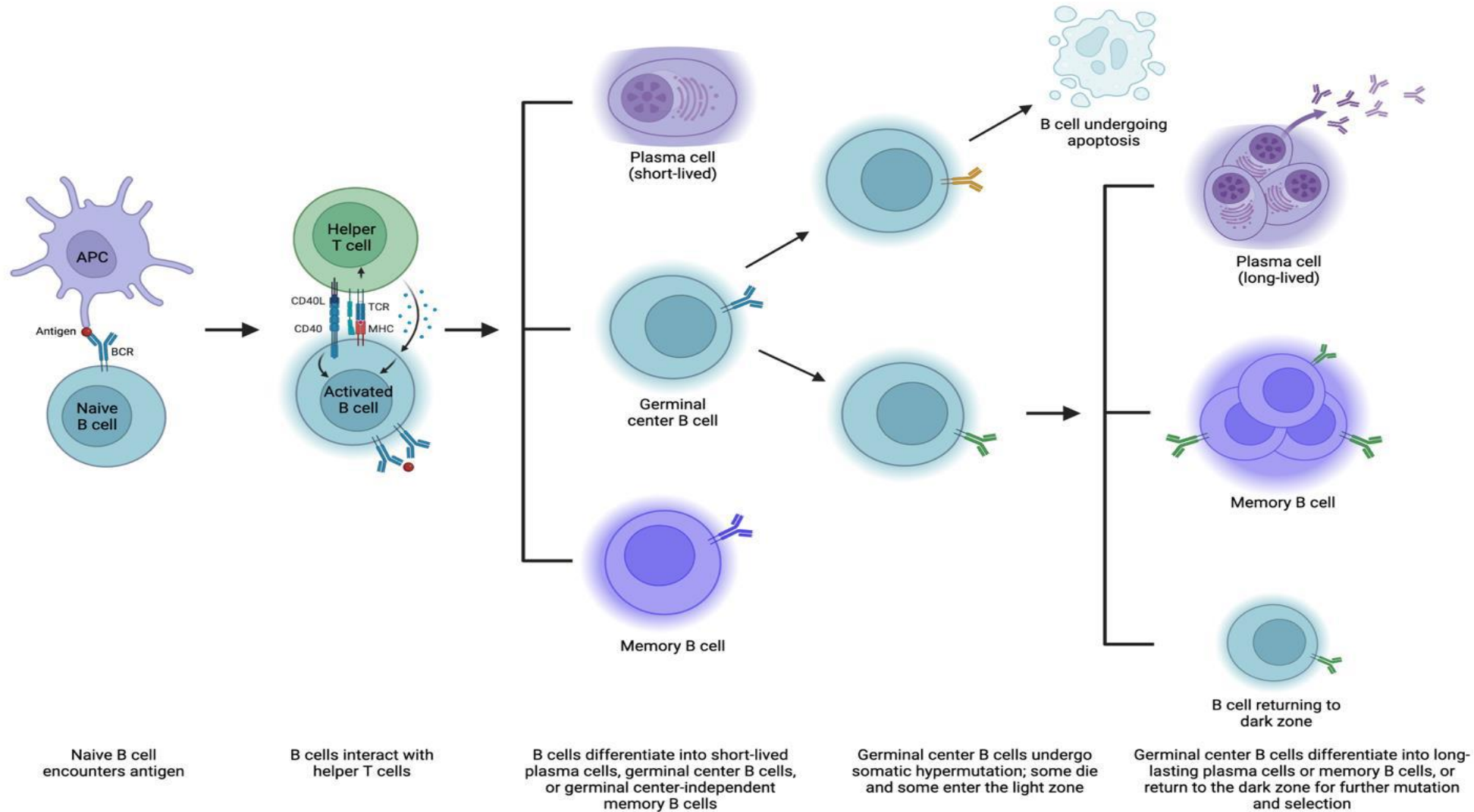


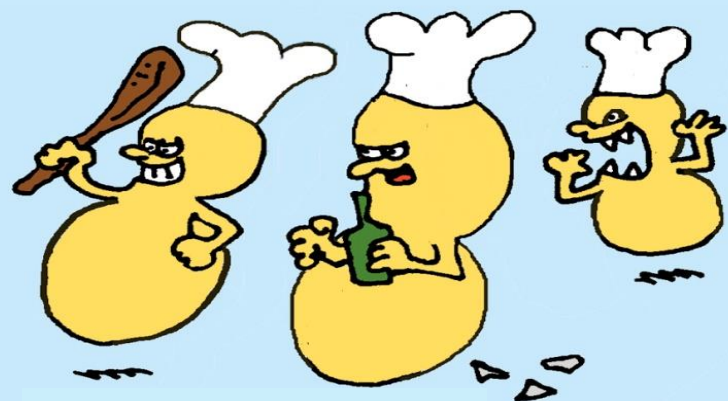
Transplantologia, Seminarium, 2025 / 2026

Odpowiedź komórkowa

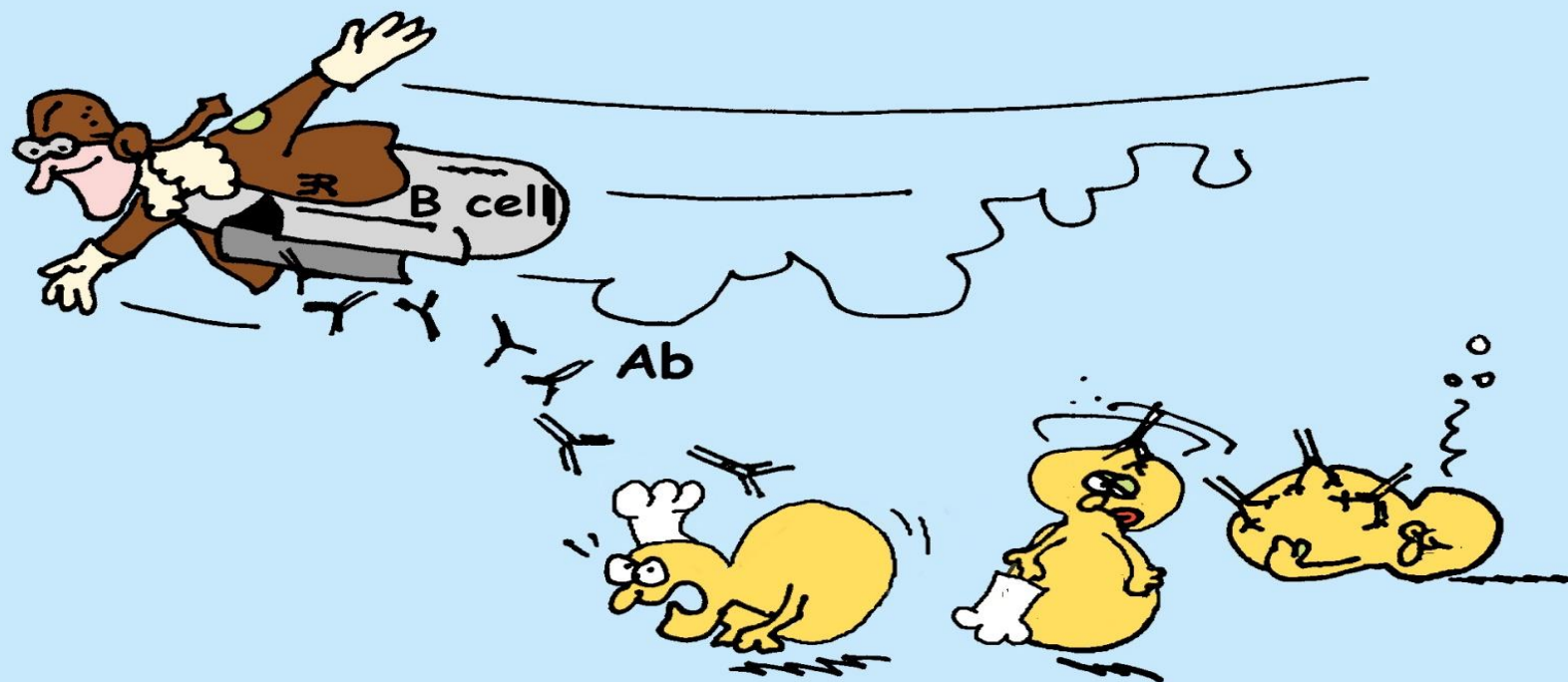
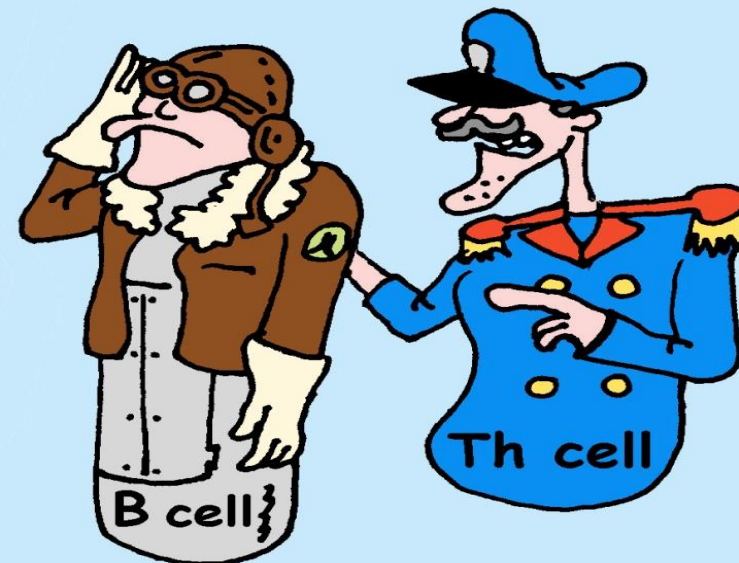


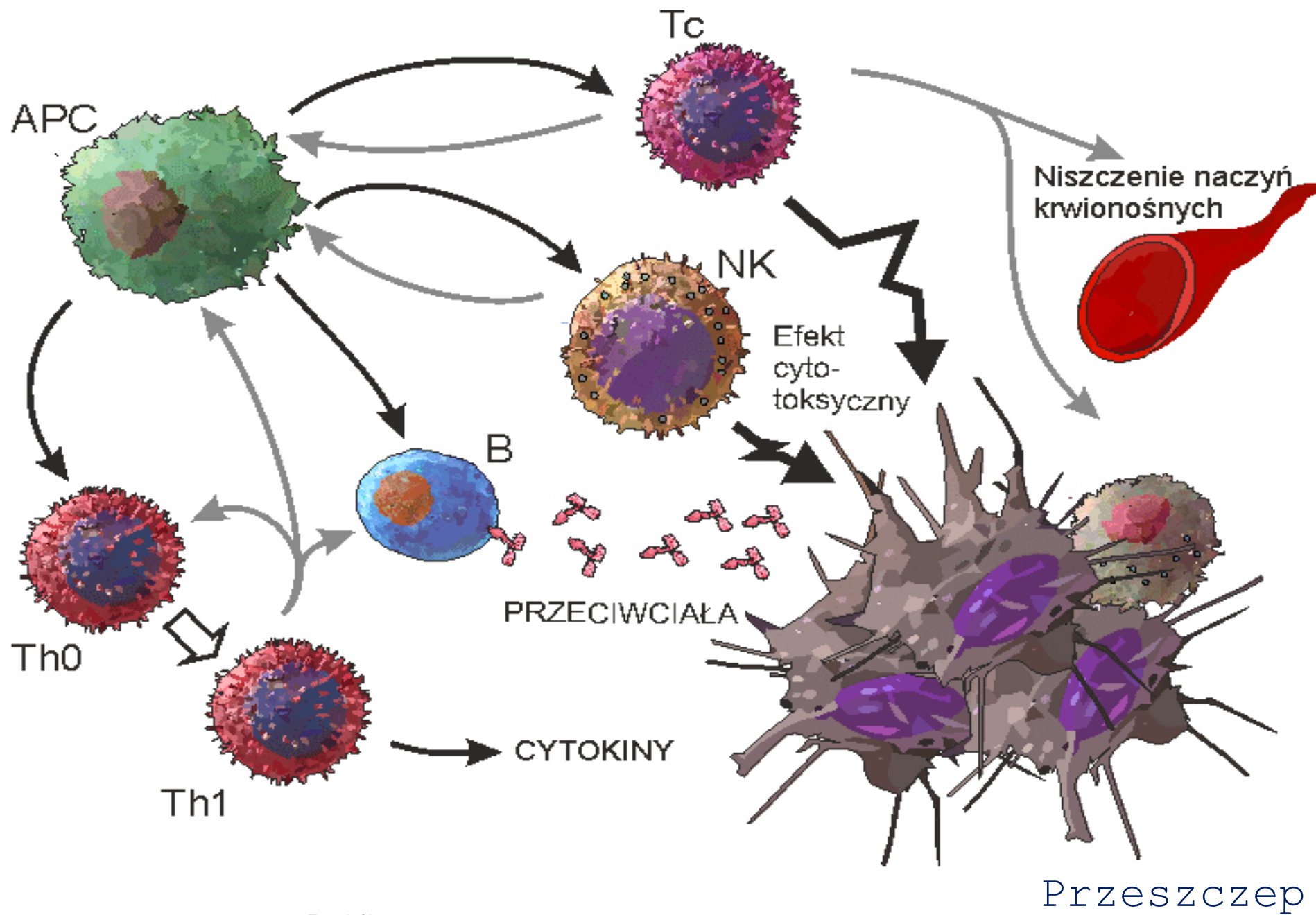
Odpowiedź humoralna





Obce antygeny





TCMR
T-Cell
Mediated
Rejection

ABMR
AntiBody-
Mediated
Rejection

Zmodyfikowano z:

Lasek W, Zagożdżon R, Jakobiśiak M. Cancer Immunol Immunother. 2014 May;63(5):419–35

Evolution and courses of rejection phenotypes*

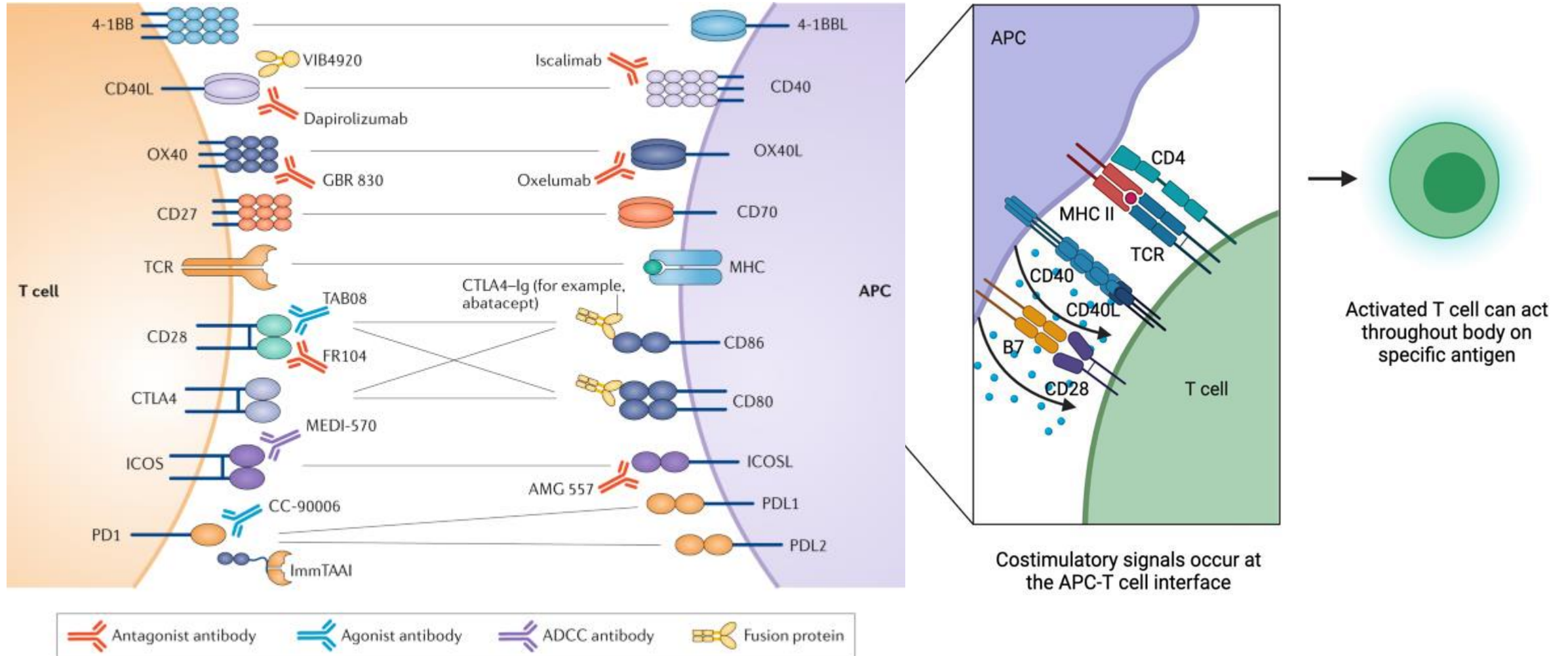
*The most common phenotype constellations are given in the table.
The table is not complete and neither reflecting all possible and observed phenotypes under real world clinical conditions.



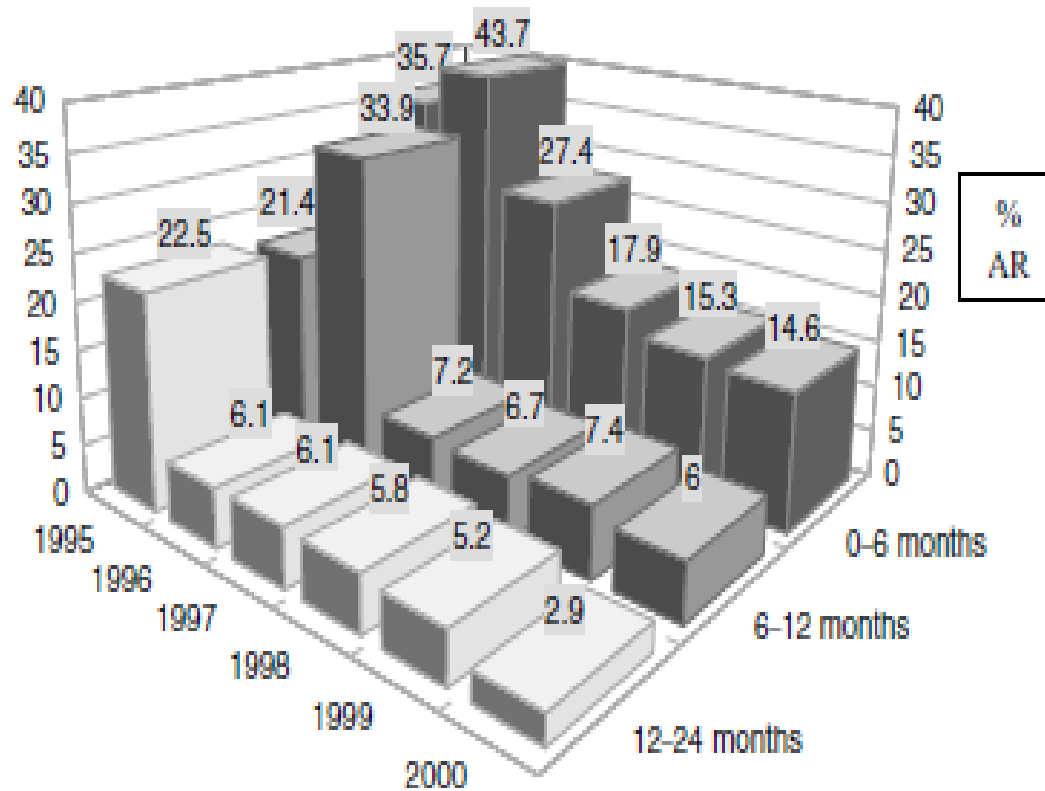
Phenotypes*	Early acute subclinical or clinical	Acute subclinical or clinical	Chronic-active subclinical or clinical	Chronic subclinical or clinical
Clinical phenotype Immunological risk Missing self	<1 month post Tx Presensitization High immunological risk: eplet mismatch or missing self	Usually clinically apparent, but can be subclinical Indicator of inappropriate immunosuppression	Slope of functional deterioration with acute/active episodes Indicator of inappropriate immunosuppression: non-compliance, medically indicated, or enhanced immune-response (cellular and/or humoral)	Stable but impaired function Often proteinuria Increased risk for recurrent / de novo renal disease
Histologic phenotype Banff lesion scores Biomarkers, C4d	Banff i and t >0; C4d0 Banff ptc and g >0; C4d +(mostly) Banff v = 0 or >0 AKI; all Banff scores = 0 / below Banff thresholds for rejection	Banff i and t >0; C4d0 Banff ptc and g >0; C4d +(mostly) Banff v = 0 or >0 Banff ci and ct = 0	Banff i and t >0; C4d0 Banff ptc and g >0; C4d - (mostly) Banff v = 0 or >0 Banff ci, ct, cg, and/or cv >0 Banff i-IFTA, t-IFTA >1	Banff i and t <2; C4d0 Banff ptc + g <2; C4d0 Banff v = 0 Banff ci, ct, cg, and/or cv >0 Banff i-IFTA <2
Molecular phenotype Rejection probabilities Injury burden	High inflammatory burden (TCMR probability) and high injury burden with or without endothelial injury (AMR probability)	Variable inflammatory burden (TCMR probability) and injury burden with or without endothelial injury (AMR probability)	Variable inflammatory burden (TCMR probability) with persisting injury burden with or without endothelial injury (AMR probability)	Low inflammatory burden (TCMR probability) and injury burden with or without low endothelial injury (AMR probability)
Serologic phenotype DSA (titer and attributes)	High titers, donor-specific Cross match positive Complement fixing/activating	High titers, donor-specific Cross match negative, but memory rebound Complement fixing/activating	Mid to low titers, donor-specific Cross match negative No complement fixing Non-HLA antibodies	Often DSA negative



Blokada kostymulacji



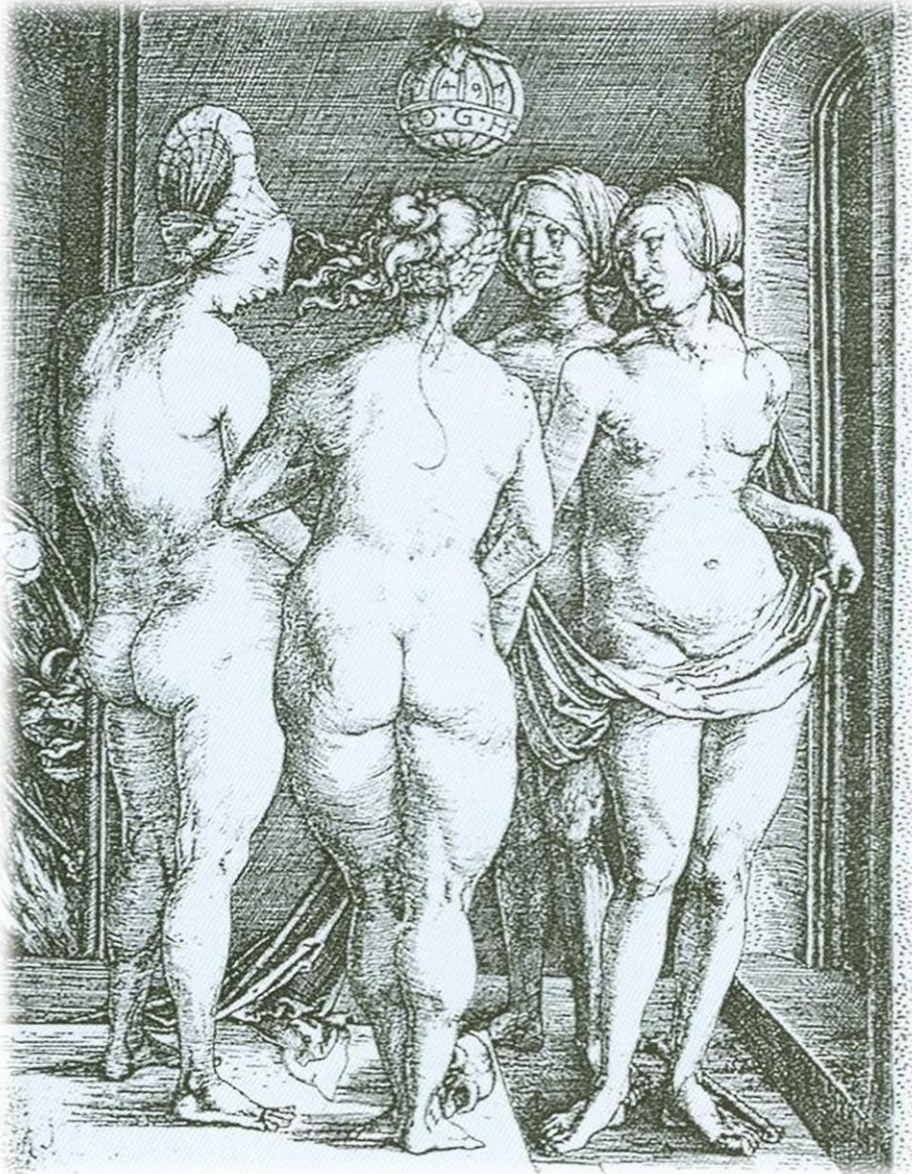
Ostre odrzucanie nerki i śmiertelność



	Przeszłość	Teraźniejszość
Ostre odrzucanie	70%	15%
Śmiertelność		↑ 14%

VR. Dharnidharka et al. Am J Transplant 2004; 4: 378

„The Four Witches”. Duerer, 1497



zakażenia

nowotwory

5-10 x częściej niż populacja ogólna
po 20 latach ryzyko >50%

cukrzyca

5-20% w ciągu pierwszego roku

choroby krążenia

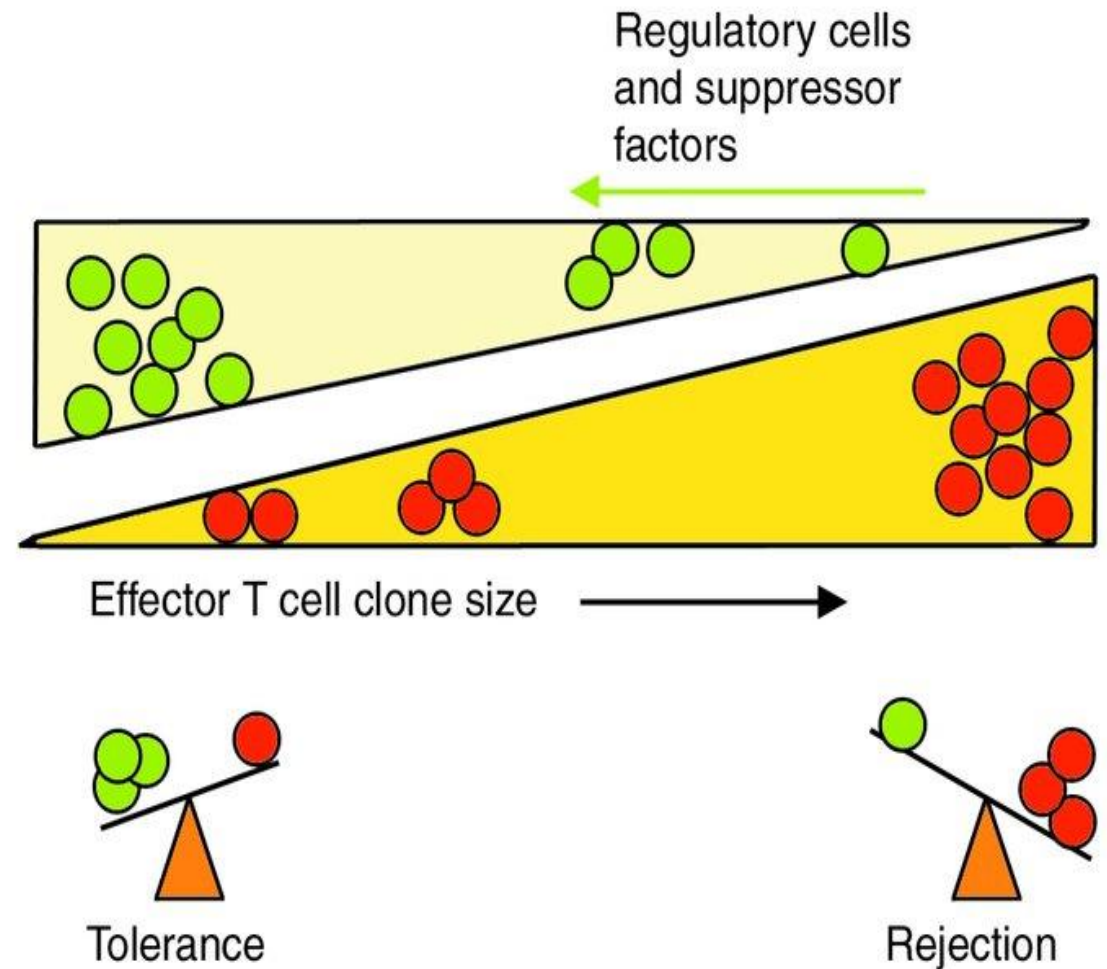
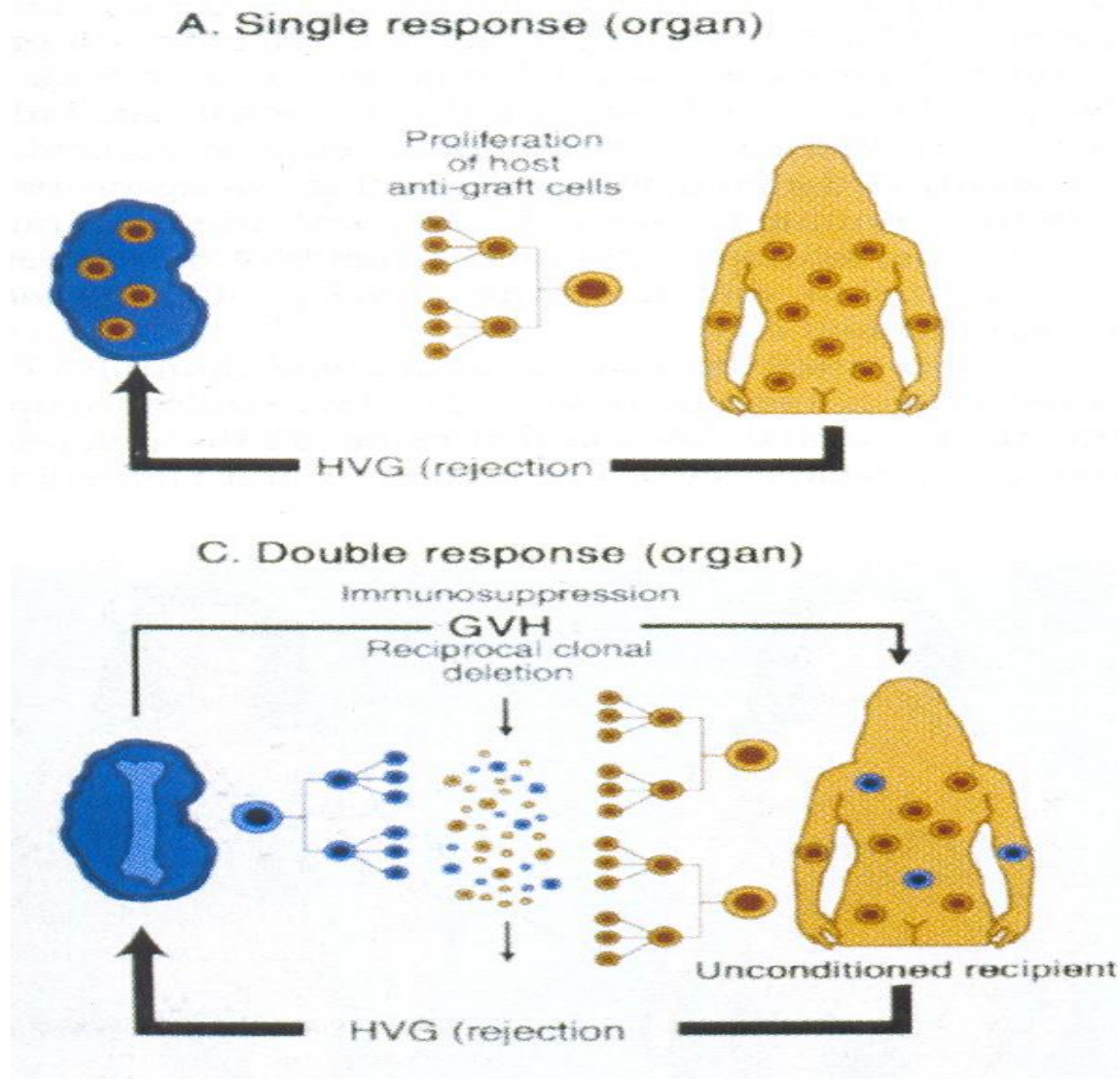
przyczyna 30-40% zgonów z czynnym przeszczepem
po 15 latach częstość:

ch. wieńcowej – 23%

ch. naczyń mózgowych – 15%

ch. naczyń obwodowych – 15%

Odrzucanie, GvHD i himeryzm

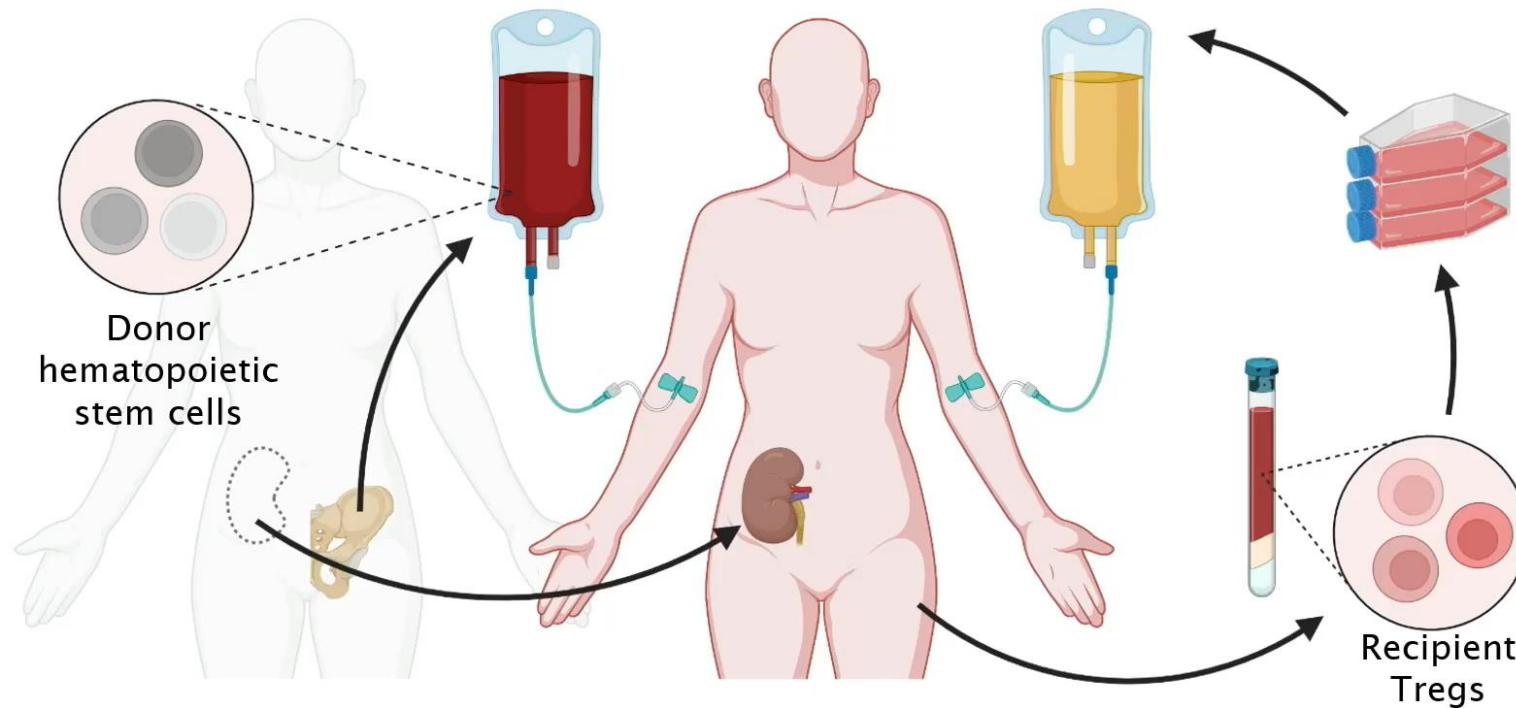


Badanie kliniczne fazy I/IIa

Dawca żywy
Brak zgodności HLA

Biorca, Tregs w 3 dobie po KTx
3 tyg Tocilizumab (α -IL6R), ATG, belatacept, SIR, steroidy

CKBMT & autologous Treg for mixed chimerism



Non-compliance po transplantacji nerki

0041-1337/04/7705-769/0

TRANSPLANTATION

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FREQUENCY AND IMPACT OF NONADHERENCE TO IMMUNOSUPPRESSANTS AFTER RENAL TRANSPLANTATION: A SYSTEMATIC REVIEW

JANET A. BUTLER,^{1,4} PAUL RODERICK,² MARK MULLEE,² JUAN C. MASON,³ AND ROBERT C. PEVELER¹

**325 Badań → 22.3% pacjentów
odstawia leki**

Objawy ogólne – odrzucanie nerki

- Wzrost temperatury bez cech infekcji
- Pogorszenie kontroli ciśnienia tętniczego
- Zmniejszenie diurezy
- Dolegliwości bólowe w okolicy przeszczepu
- Tkliwość uciskowa okolicy przeszczepu
- Powiększenie nerki przeszczepionej

Najczęściej:

BRAK OBJAWÓW !!!

rozpoznanie na podstawie
biopsji wykonanej z
powodu wzrostu stężenia
kreatyniny

56 letni
mężczyzna,
KTx IX 2005

BIOPSJA



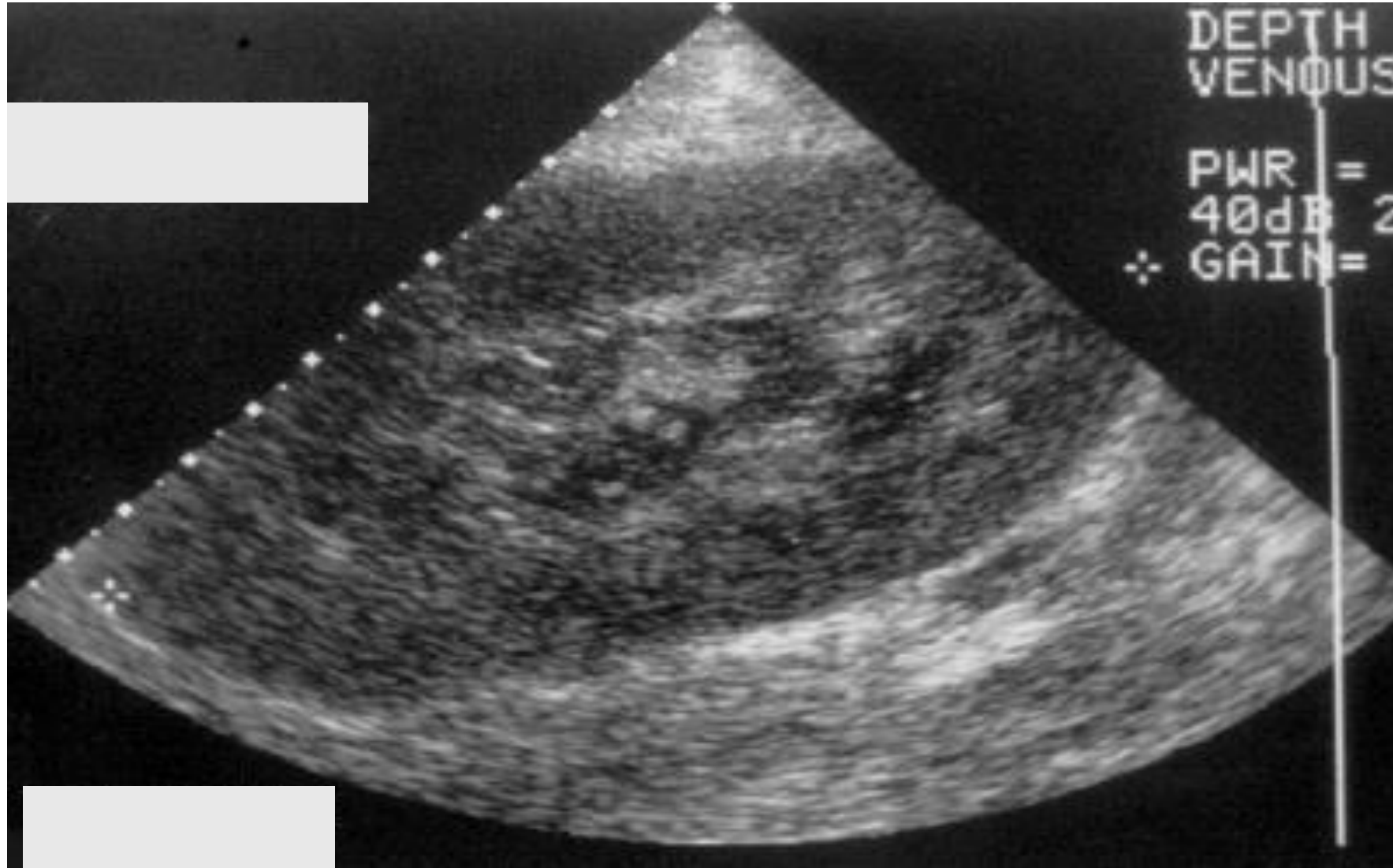
METYLOPREDNIZOLON

Data	28.10.05	30.10.05	1.11.05.	2.11.05	3.11.05	4.11.05	5.11.05	
Biopsja					0,5 g i.v.	0,5 g i.v.	0,5 g i.v.	
Ciśnienie t.	145/80	155/75 120/60	137/71	100/60 130/80	130/80	127/72		
Masa c./Temp.	82,4/N	81,0/N	78,0/N	79,3/N	/N	80/N		
	osocze	mocz	osocze	mocz	osocze	mocz	osocze	mocz
Sód mmol/L	137		134	132/132	135/128/131	138	143	145
Potas mmol/L	4,7		6,3	5,9/6,2	5,5/7,3/5,6	5,3	5,4	5,0
Wapń mmol/L	10,1		10,3		10,6		11,4	
Fosfor mmol/L							mp-1,9 pocp-2,7	
Chlor mmol/L	mp-1,7		mp-1,5					
Wodoroweg. HC03 mmol/L	25,2		24,9		25,3/20,6/26,2	27,5	28,1	23,0
Kwas moczowy mg%								
BUN mg%								
Kreatynina	1,2	1,4	1,6	1,9↑	1,9	2,6	2,0↓	
Diureza	4200	4500	6300	5500				
Białkomocz				gluk-14 mmol/l biur 0 c.ket 0				
Osad moczu				ew-1,01 pH-6,0 białko 0,20 g/l kaci-10j wpu cy-1-3 ropiszna			d-1010 pH 5,5	
Ukrwienie RPF				cTnI-0,13 (do 0,1) CK-66 (40-171) CK-MB-17 (0-25)		cTnI-0,09	cc-16C-1	
U S G				L-3-5 ropis 48Tn biur-1-2 biur-1-2			L-1-5 wpu	

USG - obrzęk i powiększenie nerki



USG: obniżenie echogeniczności warstwy korowej + obrzęk piramid (zatarcie granicy kora-rdzeń)



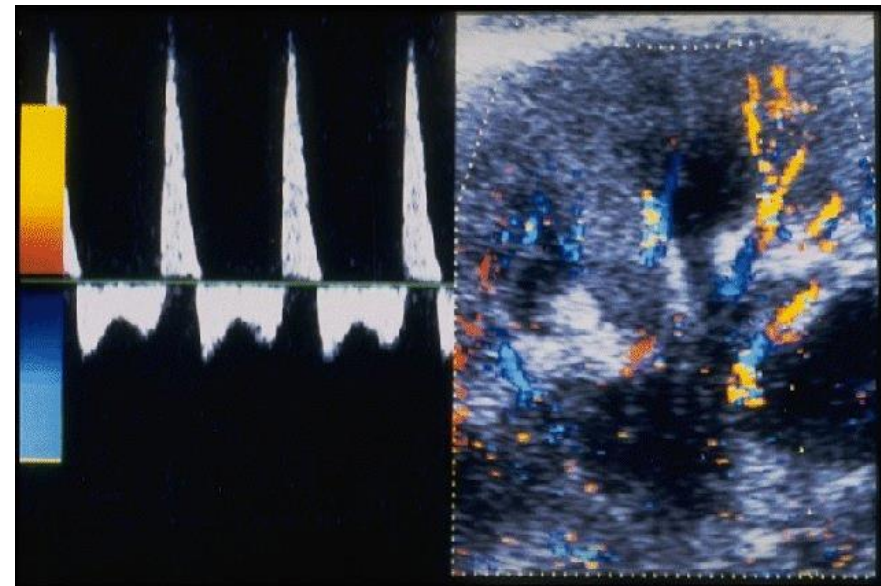
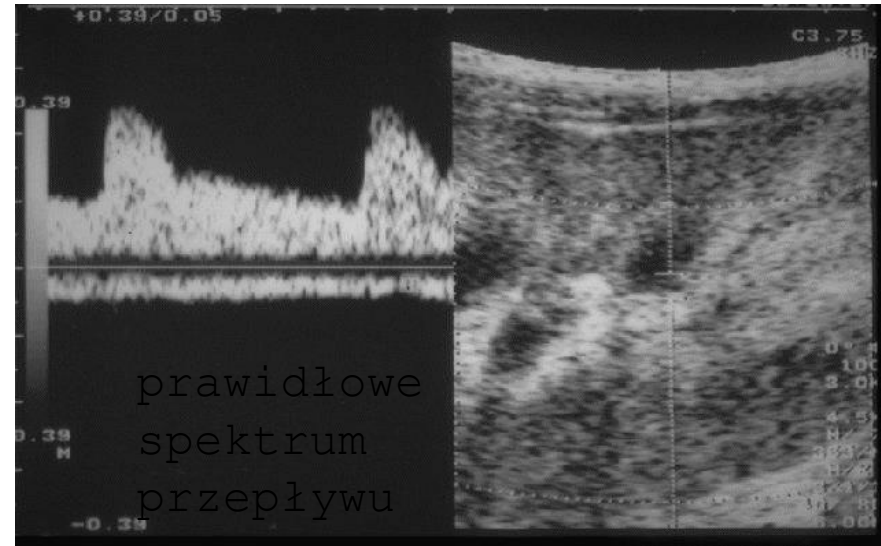
USG met. Dopplera

Zmniejszony przepływ w fazie rozkurczu, jego brak lub odwrócenie

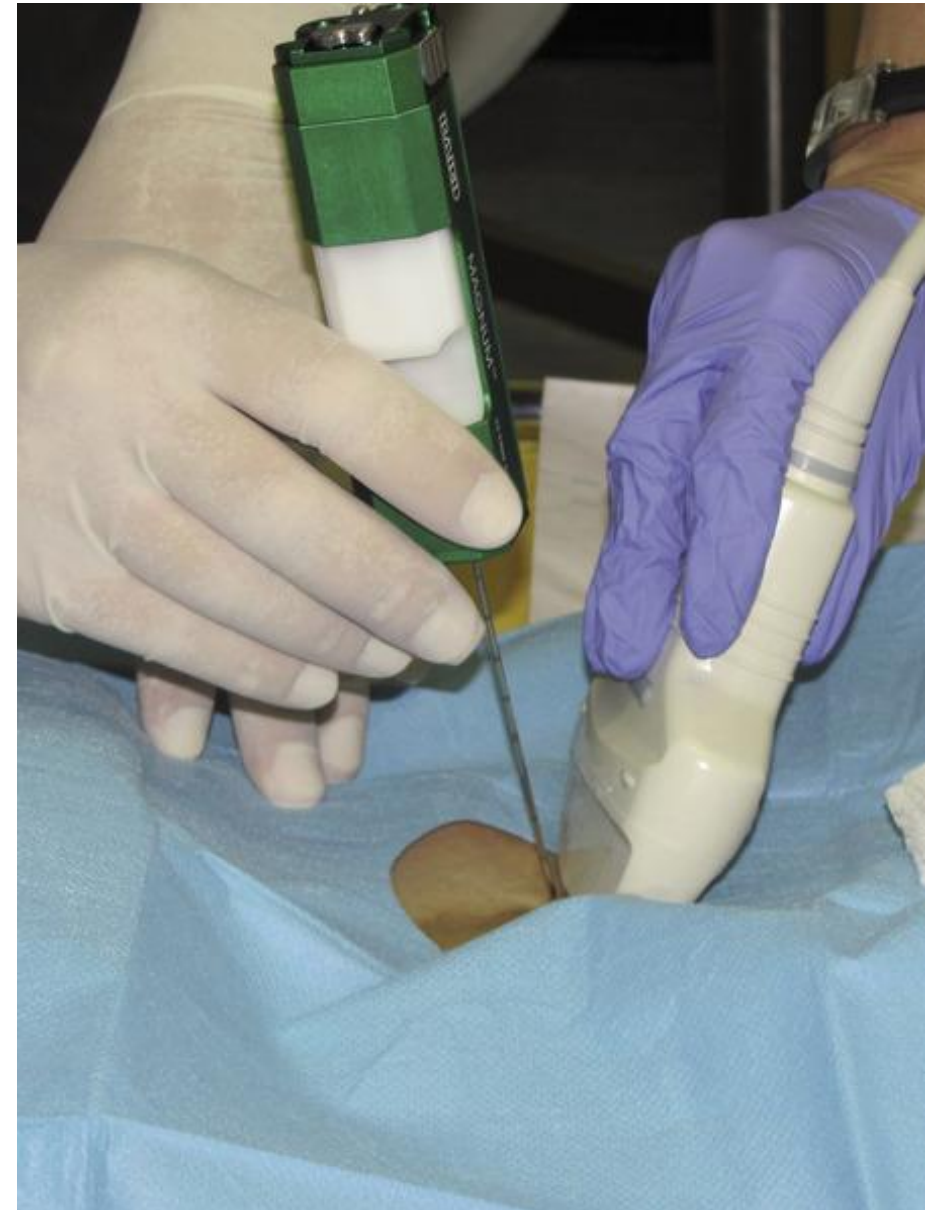
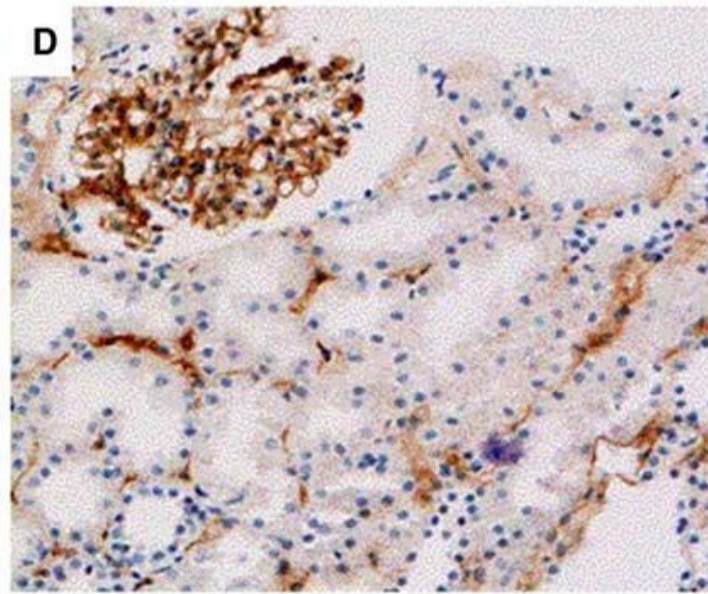
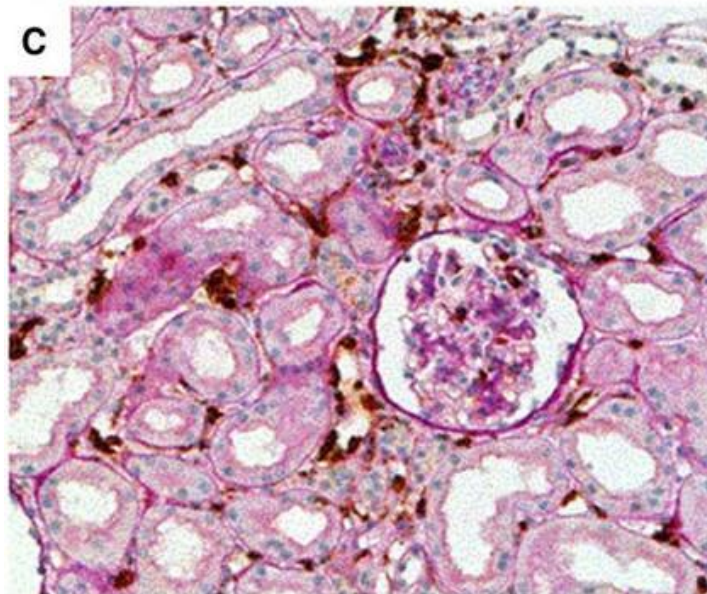
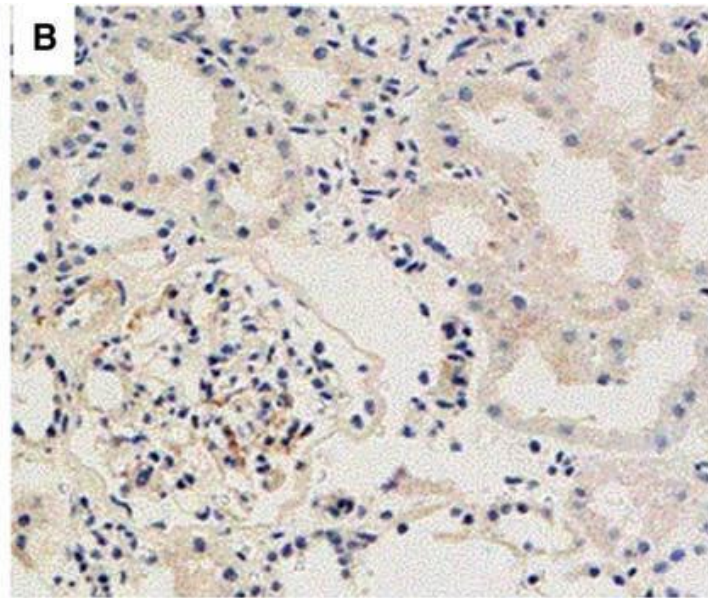
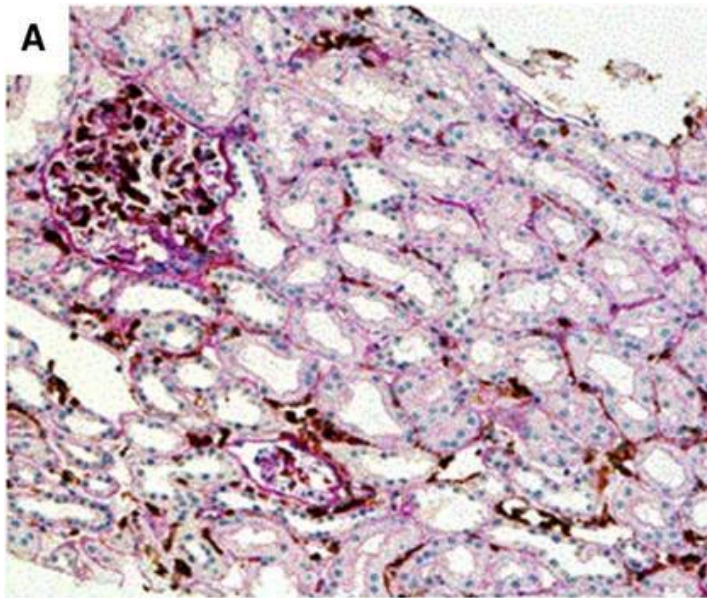
+

Wzrost wskaźników:

- oporów przepływu (RI) $> 0,8$
- pulsacyjności (PI) $\geq 1,5$



Biopsja cienkoigłowa – standard w diagnostyce odrzucania



Pierwszy dowód na możliwość zastosowania sieci neuronowych (CNN) w głębokim uczeniu po KTx

Deep learning-based histopathological assessment of renal tissue

TRAINING

- 40 transplant biopsies
- 10 tissue classes
- 9488 annotations

TEST

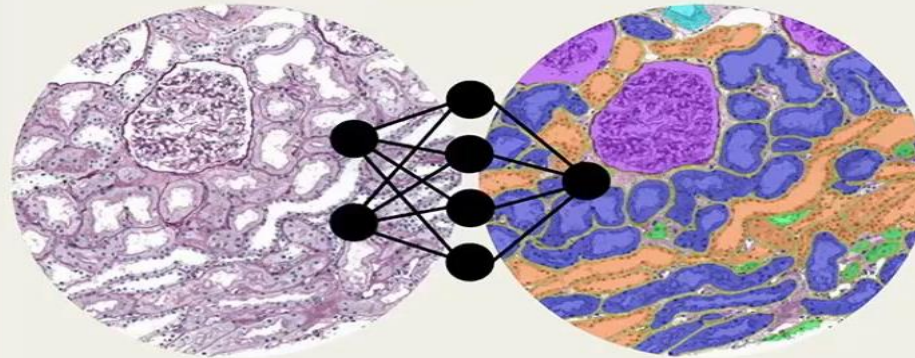
- 20 transplant biopsies from two centers
- 15 nephrectomy samples
- 82 transplant biopsies for correlation with visual (Banff) scoring of multiple pathologists

LEGEND

- Border
- Glomeruli
- Undefined tubuli
- Proximal tubuli
- Distal tubuli
- Atrophic tubuli
- Arteries

No fill = interstitium

Convolutional Neural Network for segmentation renal tissue



RESULTS

- Highest performance for glomeruli, tubuli and interstitium segmentation
- Average DC¹ 0.88
- Equal performance on images external center
- For analysis of nephrectomy and biopsy samples
- For healthy and pathological tissue
- CNN-based quantifications correlate significantly with components Banff scoring system

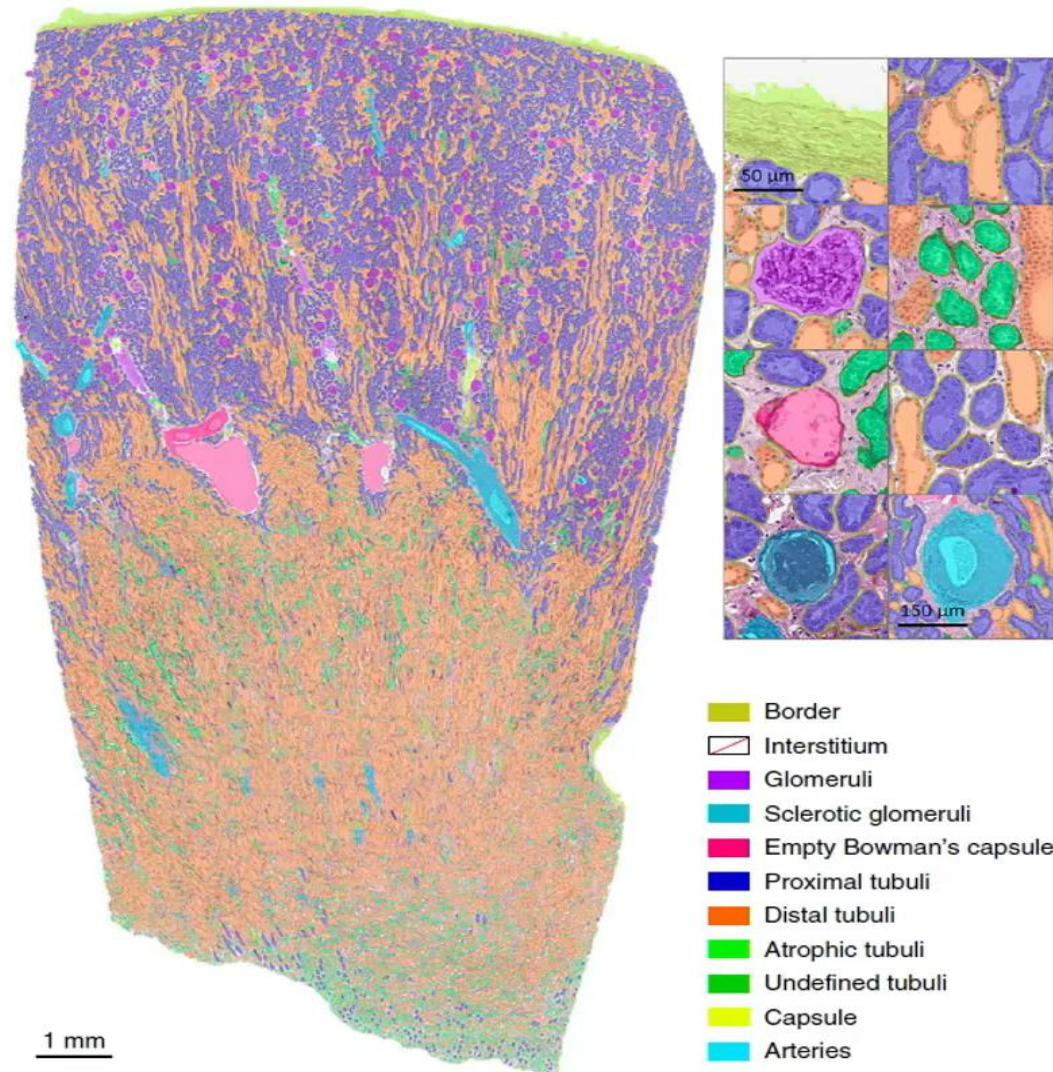
CONCLUSION

This study presents **the first CNN for multi-class segmentation** of periodic acid-Schiff-stained **nephrectomy samples and transplant biopsies**. Our CNN can be of aid for quantitative studies concerning renal histopathology **across centers** and provides opportunities for deep learning applications in routine diagnostics.

¹DC= Dice coefficient

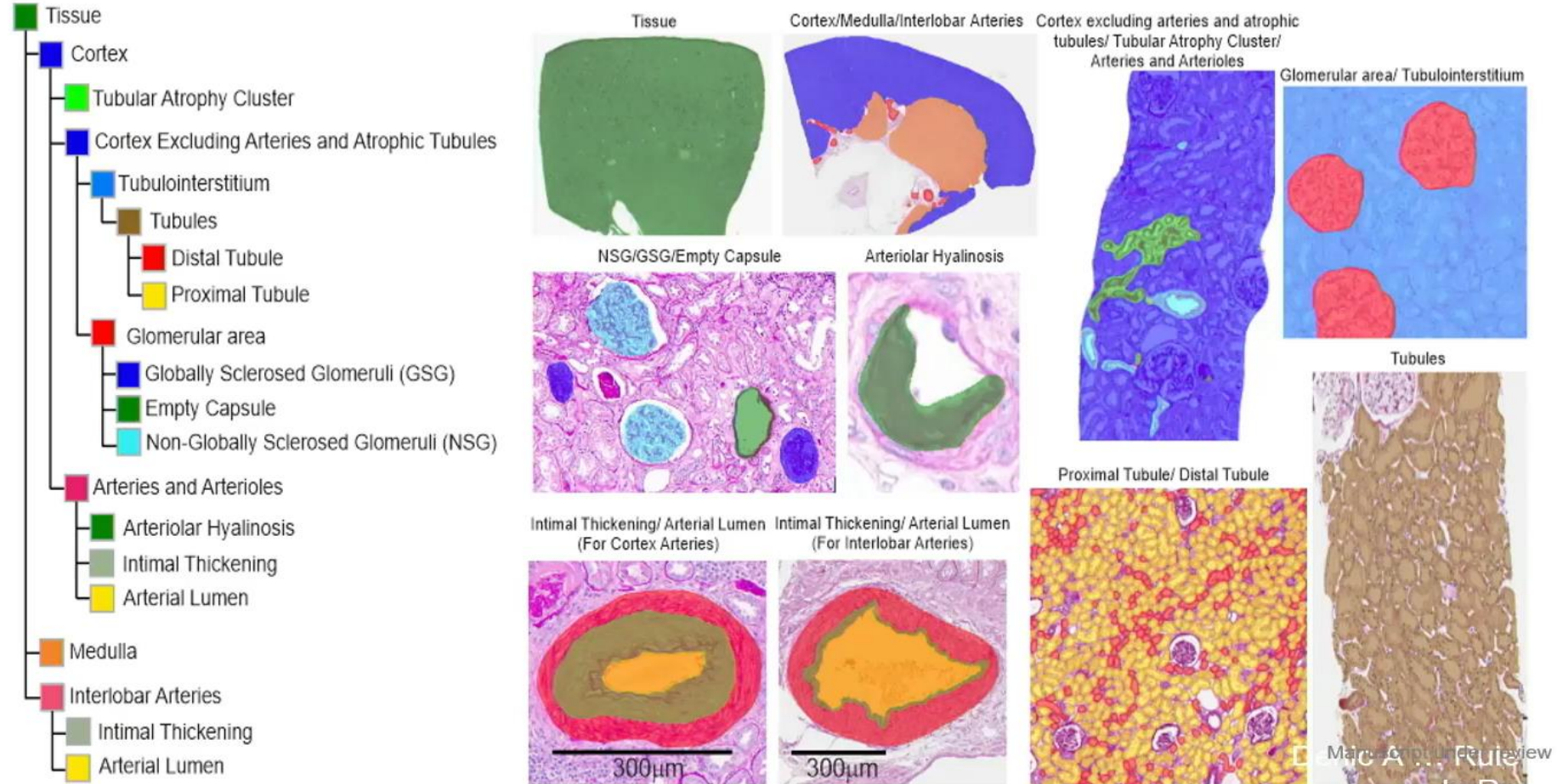
JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Pełna segmentacja z wykorzystaniem CNN



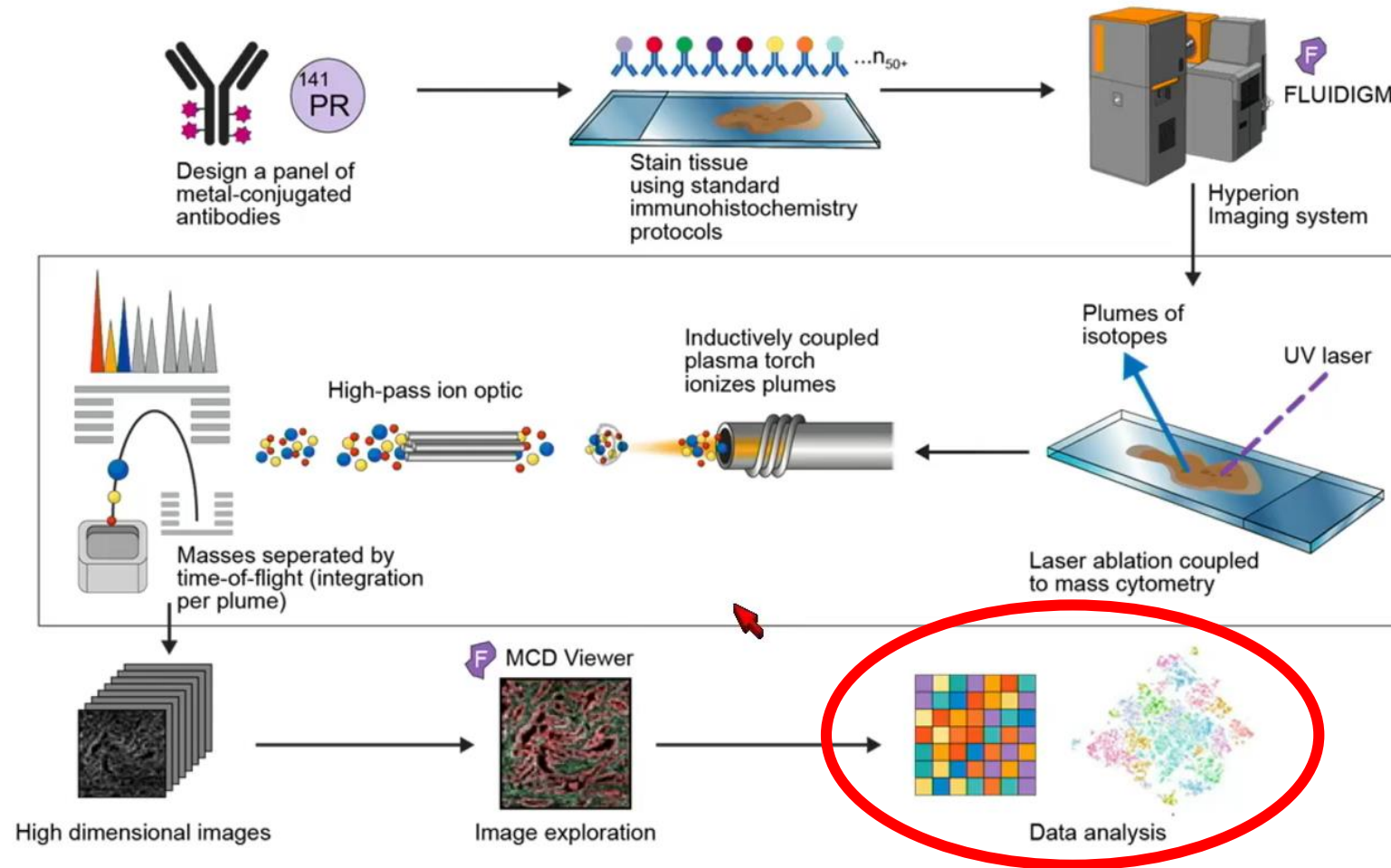
Zastosowanie AI w analizach morfometrycznych

AI – automate morphometric analysis for chronic changes

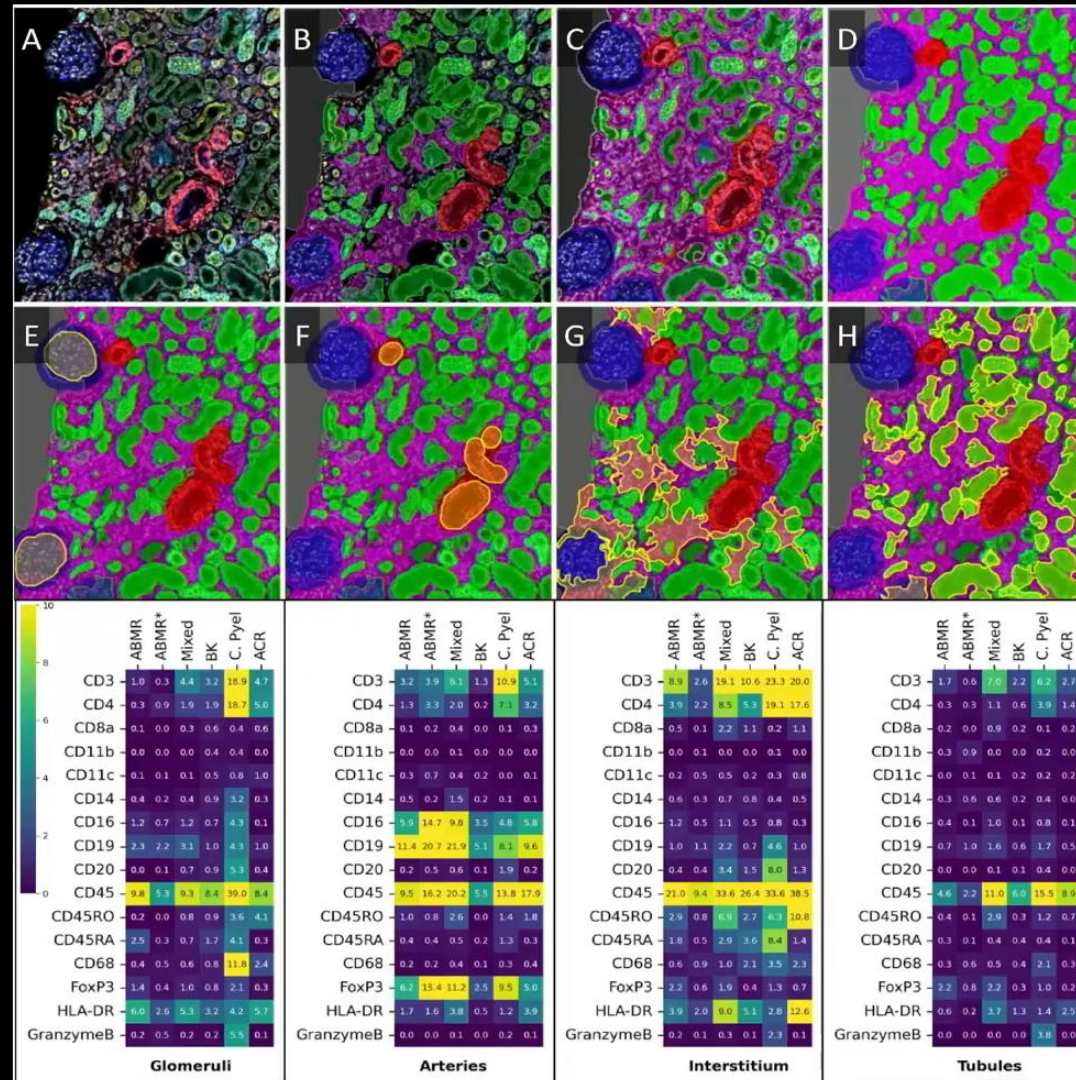


Obrazowanie z wykorzystaniem cytometrii mas

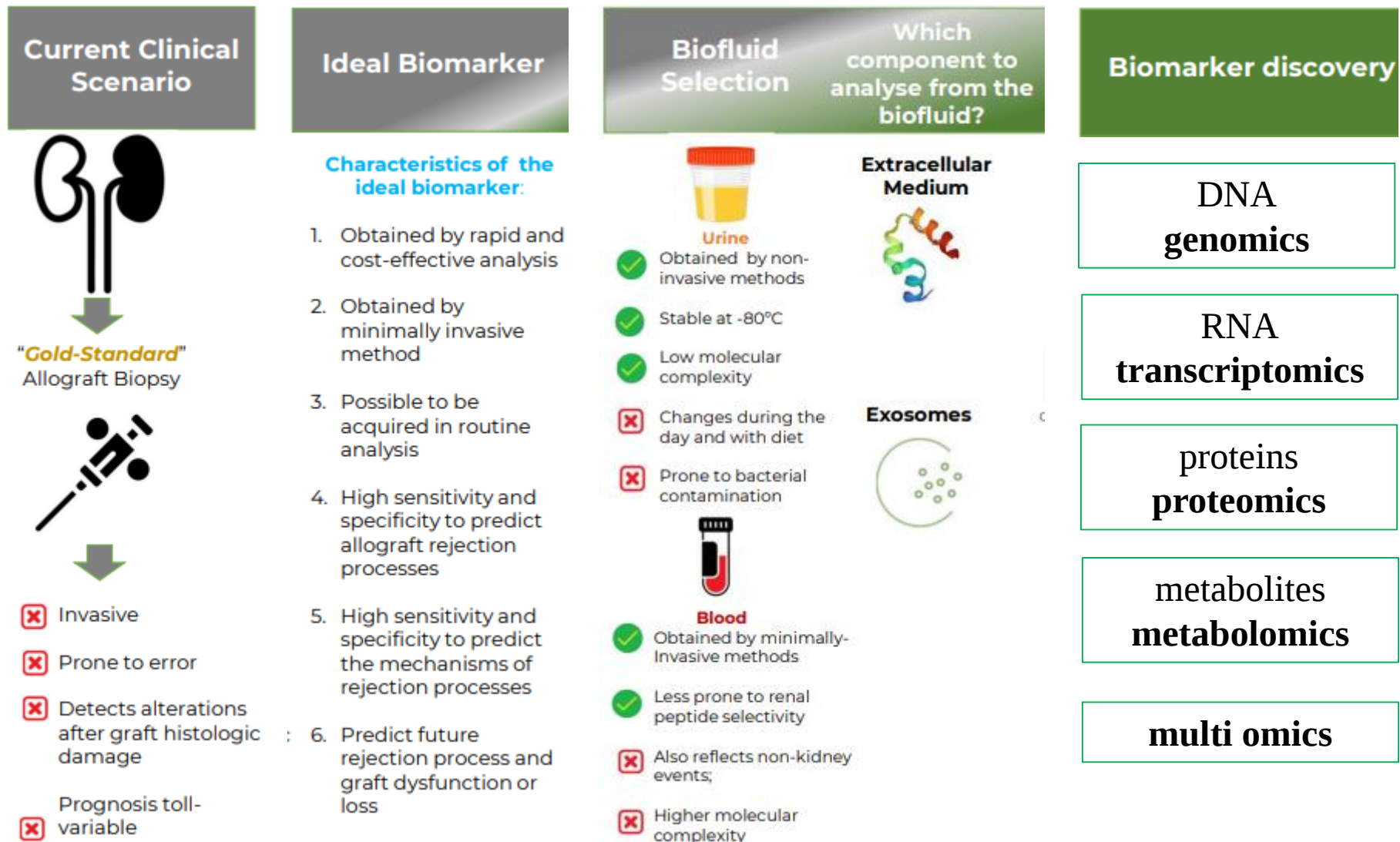
Workflow of Imaging Mass Cytometry



Jednoczesne obrazowanie do 40 białek



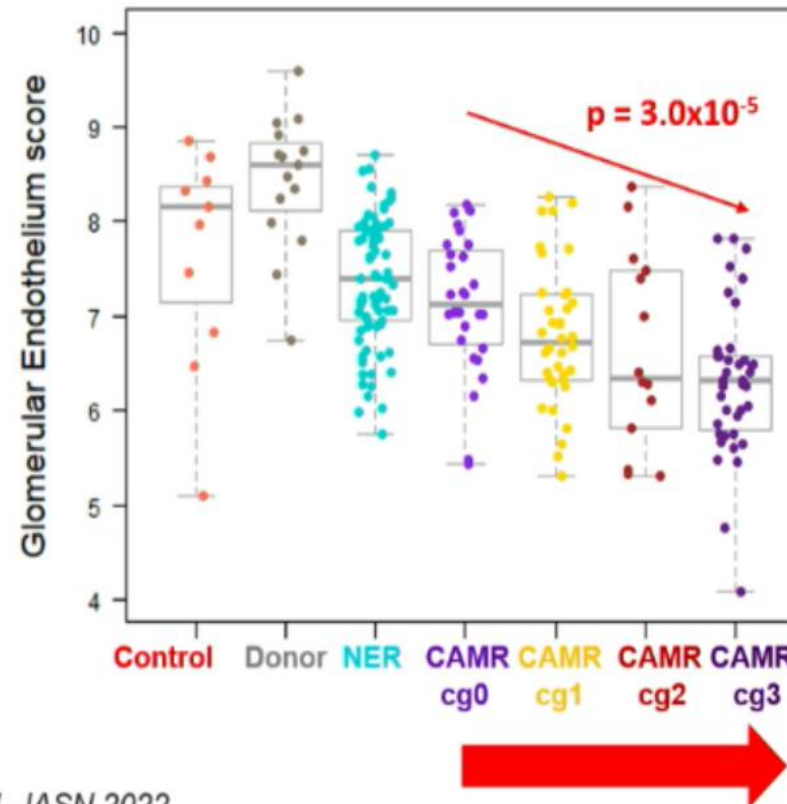
Biomarkery – materiał i metody



Analiza mRNA w przewlekłym odrzucaniu humoralnym

**Redukcja genów
swoistych dla
komórek śródbłónka
kłębuszków**

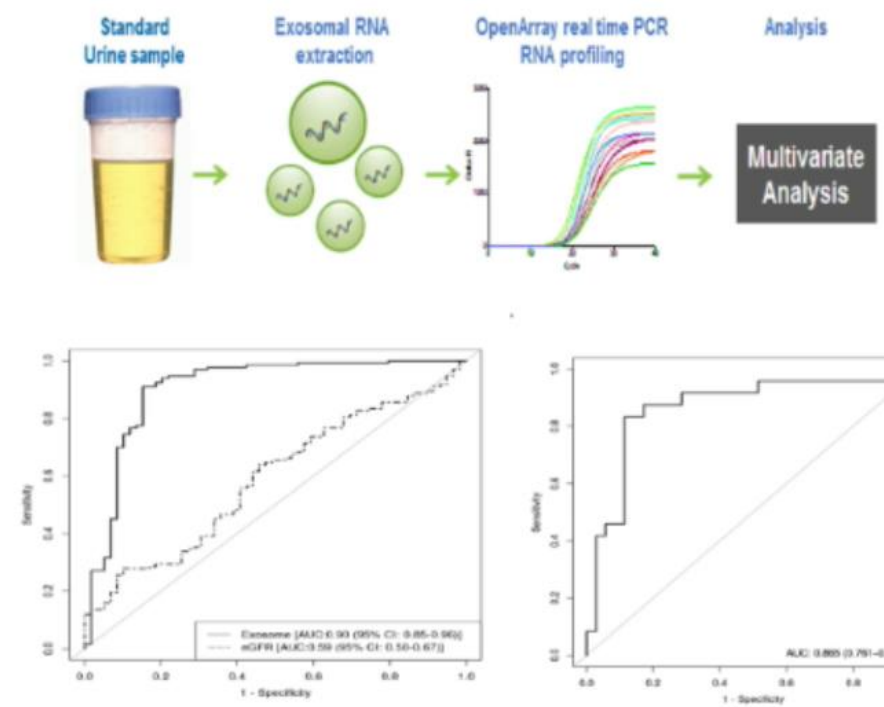
**EHD3 &
SOST**



*cg = chronic/transplant glomerulopathy
(Banff 2019 classification)

Panel mRNA egzosomów moczu w odrzucaniu i różnicowaniu ABMR i TCMR

Background

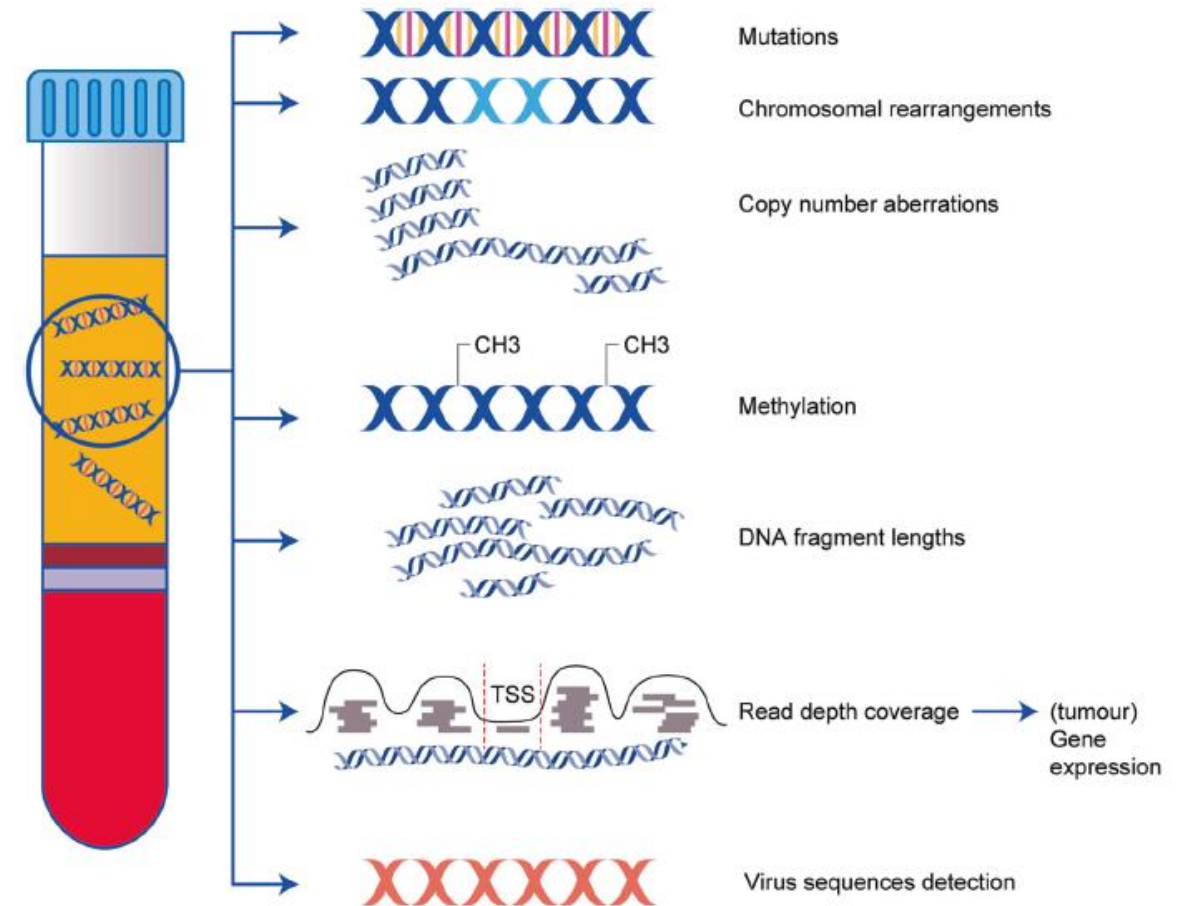
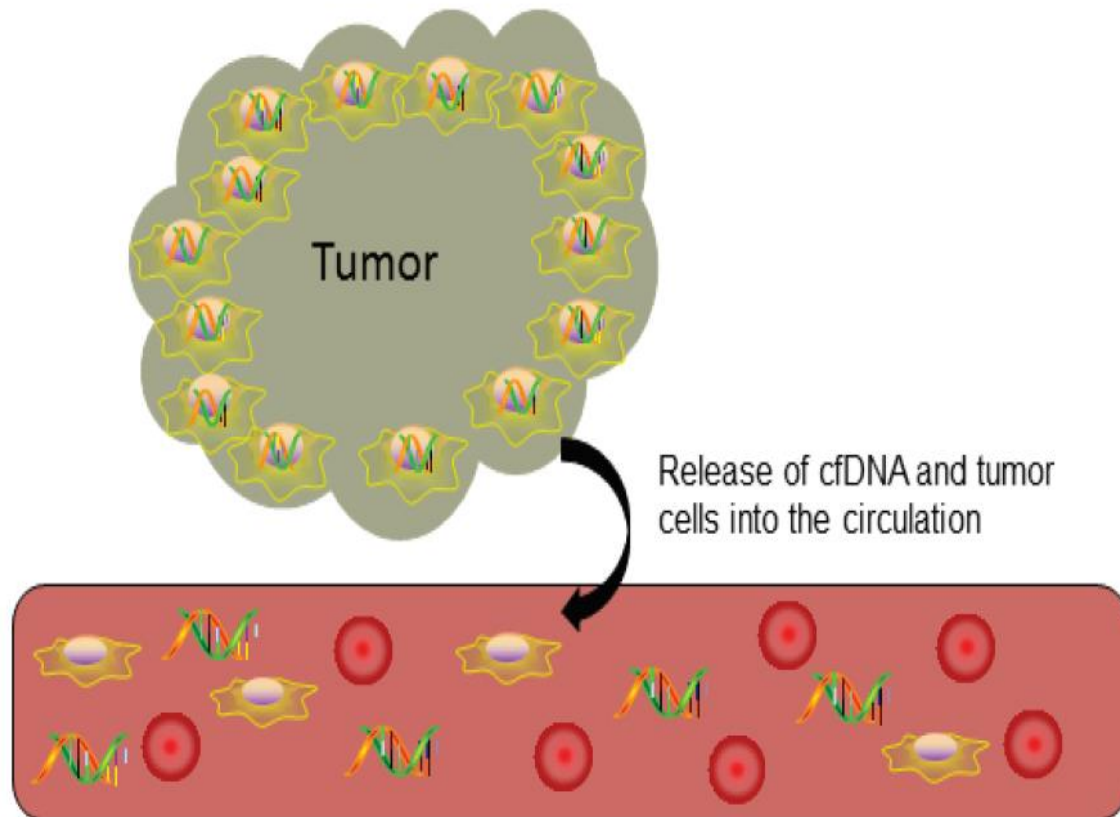


Gene Signatures	Role in immune activation
For any-cause rejection IL32, CXCL14, B2M BMP7, C3, CXCL11 CD74, PYCARD, STAT1, TBP, NAMPT, IFNGR1, IRAK2, IL18BP, SERPINA1	pro-inflammatory cytokines TGFβ superfamily Upregulated in acute allograft rejection inflammasome, different auto-immune process
For discriminating ABMR from TCMR CD74 C3, CXCL11, CD44, IFNAR2	regulating protein trafficking, dendritic cell migration and T lymphocytes homing

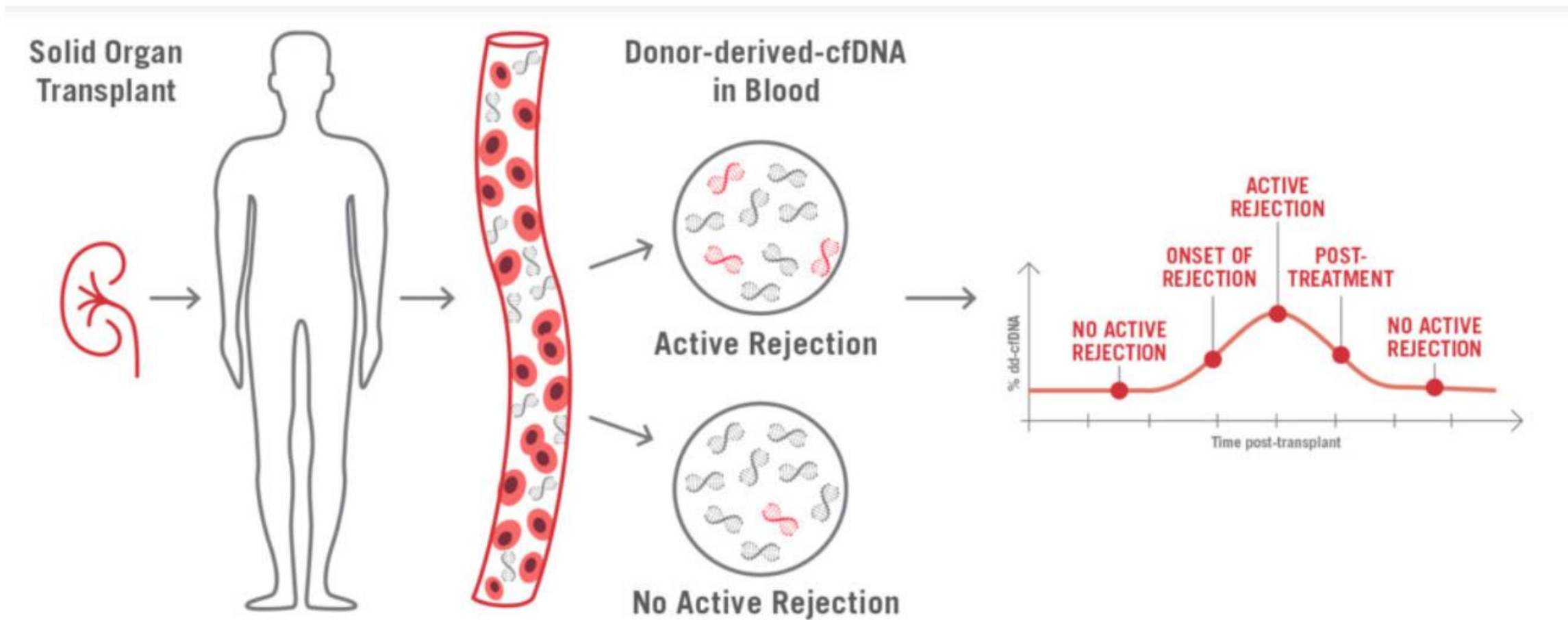
- Sen 84.7% NPV 93.1% for any cause rejection
- Sen 87.5% and NPV 90.6% discriminating ABMR from TCMR

El Fekih R, Hurley J, Azzi J. J Am Soc Nephrol. 2021 Mar 3;32(4):994–1004

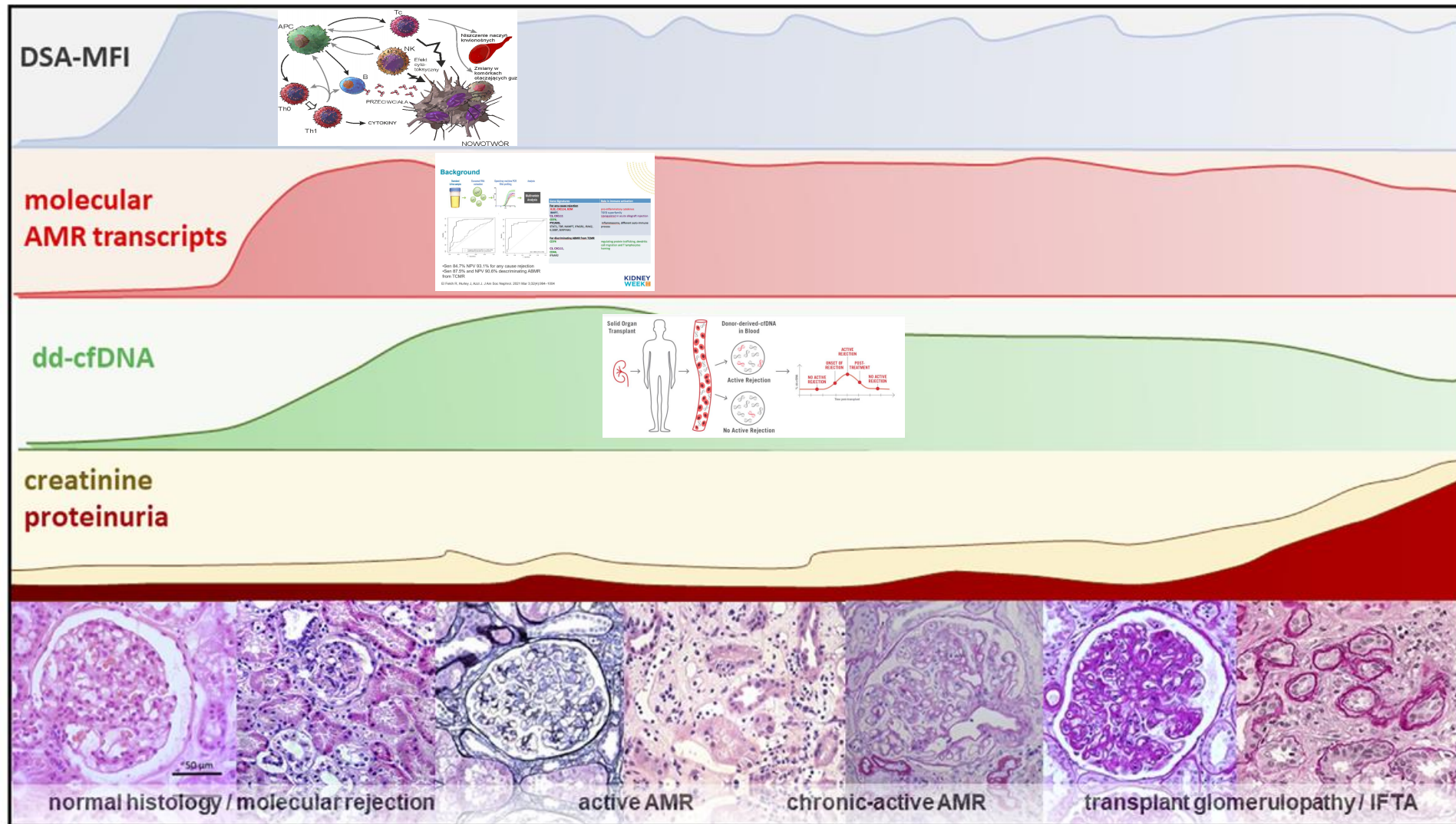
Cell free DNA w diagnostyce



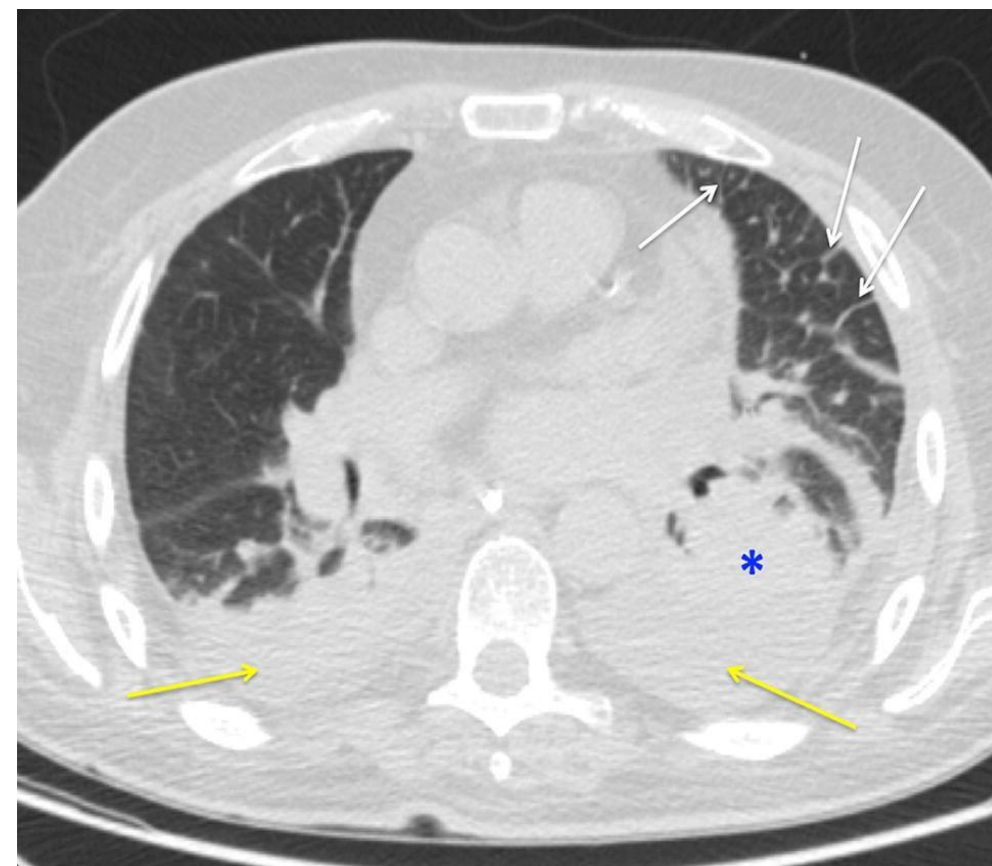
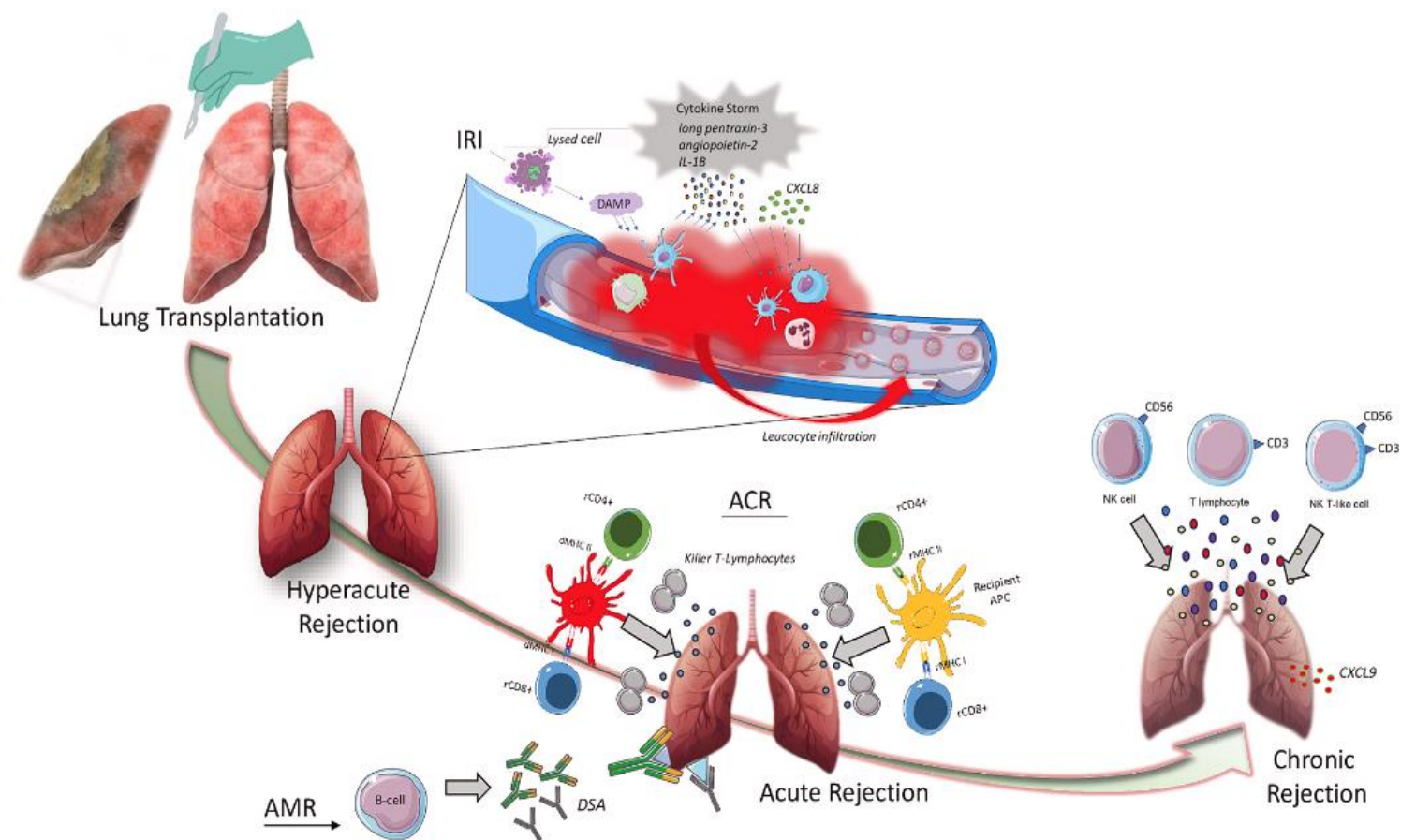
Cell free DNA w diagnostyce odrzucania



Wczesna diagnostyka ABMR

[illegible]

Odrzucanie po przeszczepieniu płuc

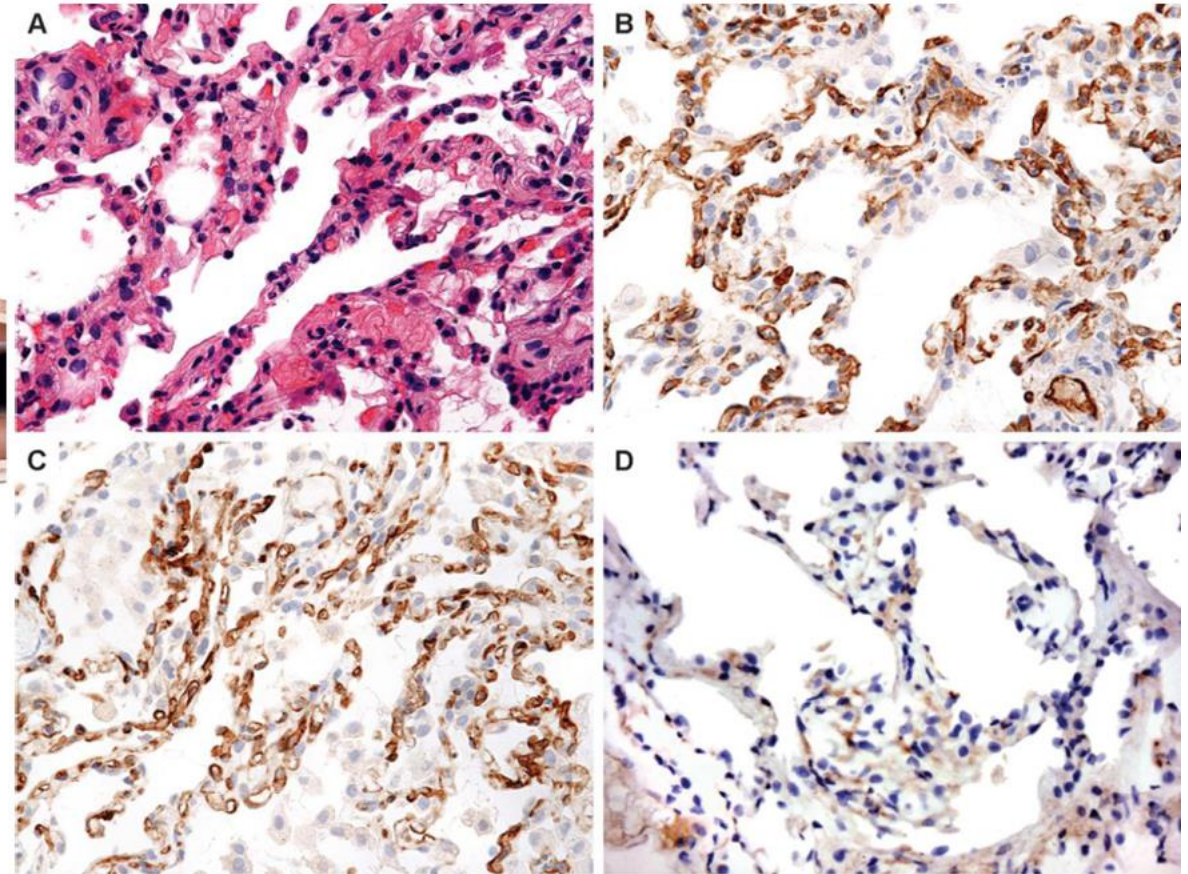
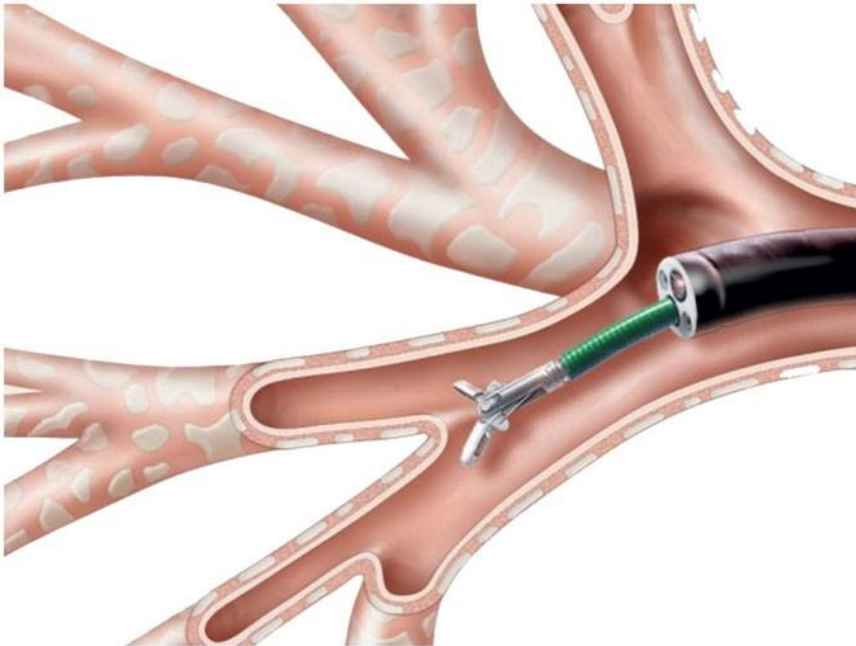


- zagęszczenia miąższowe (*)
- pogrubienie przegród międzypłatowych (białe strzałki)
- obustronny wysięk (żółte strzałki)

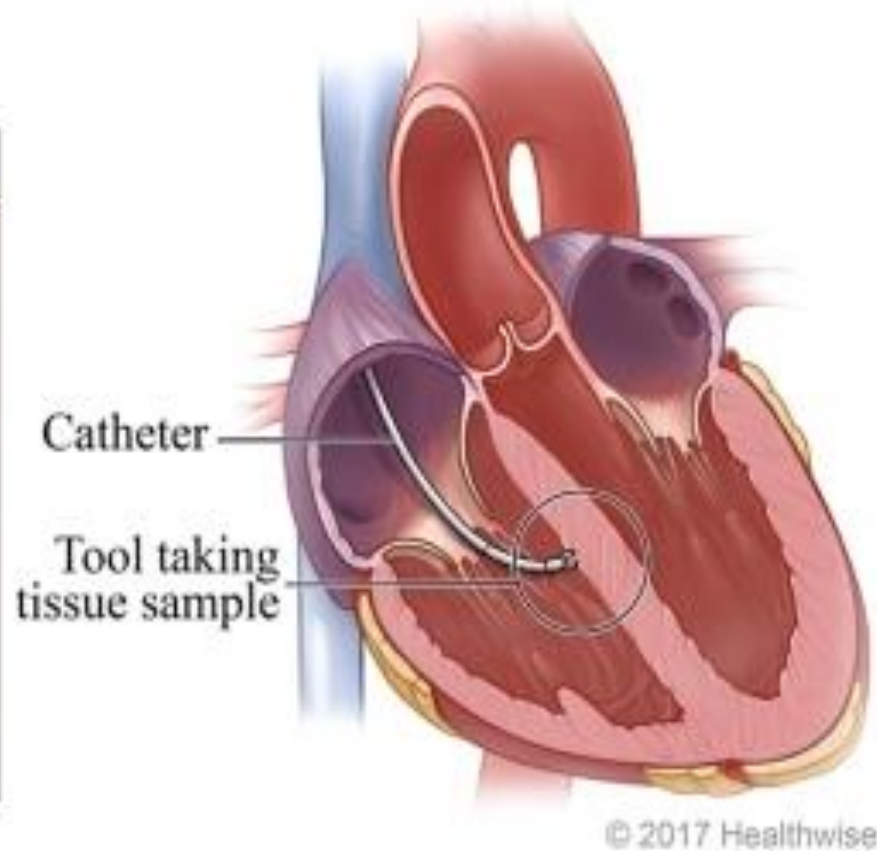
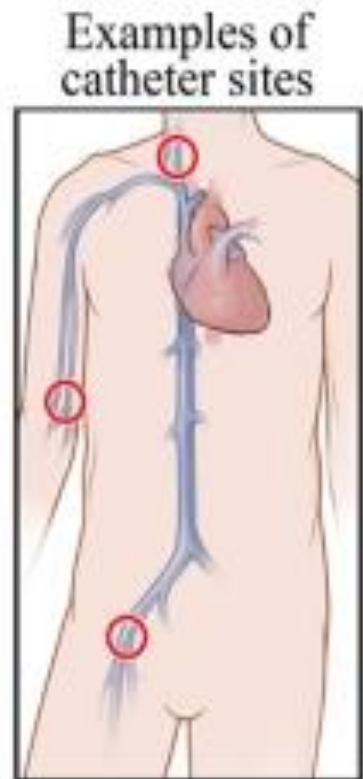
Biopsja transbronchialna - standard diagnostyczny odrzucania po przeszczepieniu płuc

A - H&E

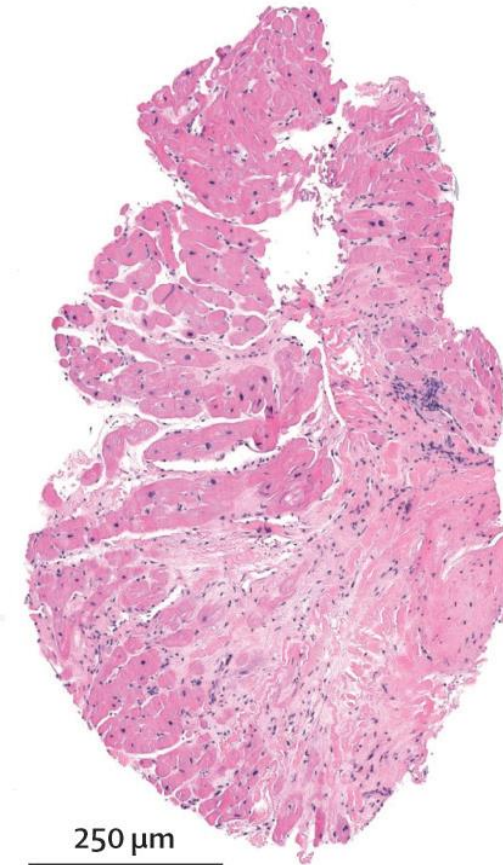
B, C - złogi C4d



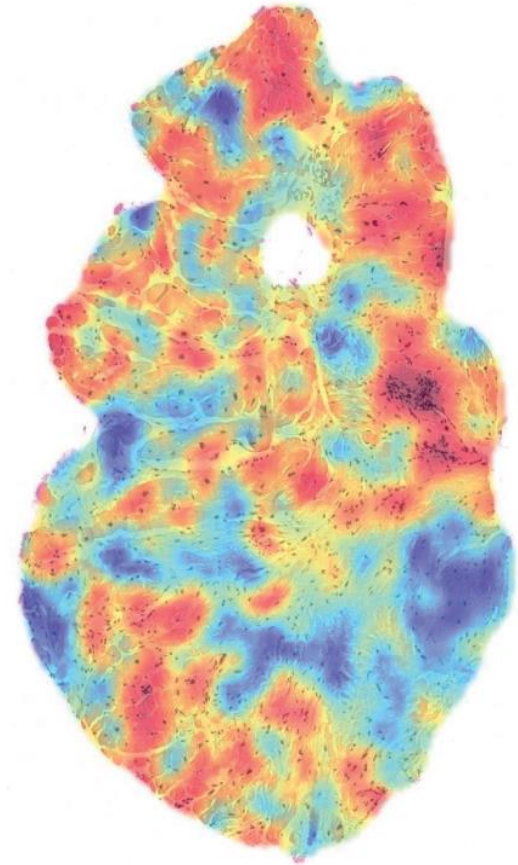
Biopsja edomiokardialna - standard diagnostyczny odrzucania po przeszczepieniu serca



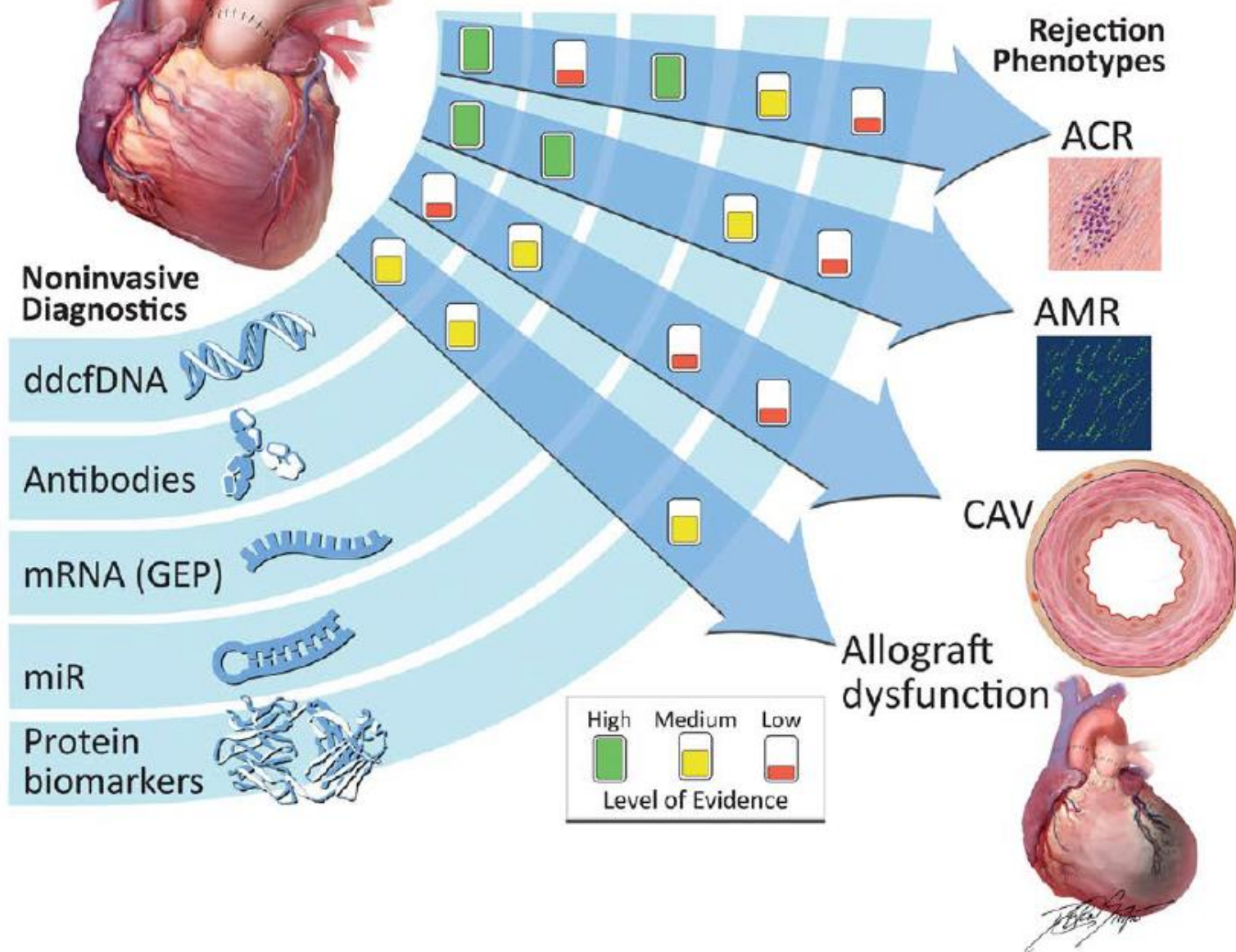
Haematoxylin and eosin stained tissue



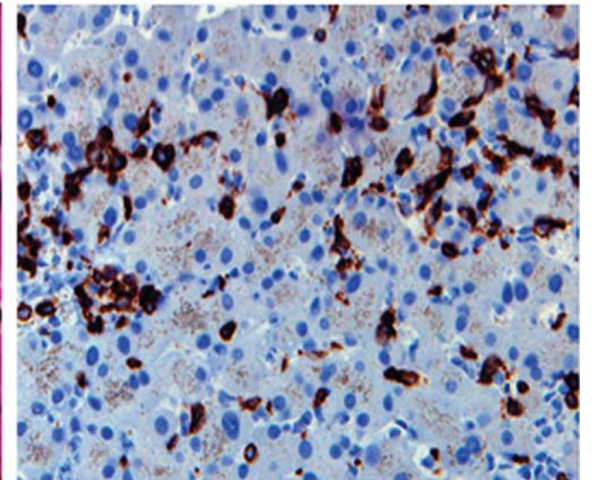
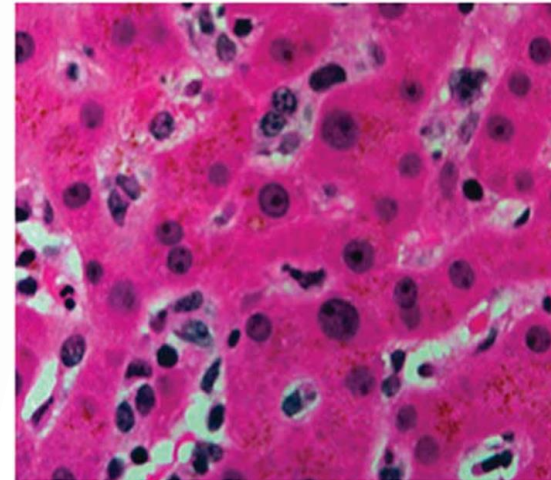
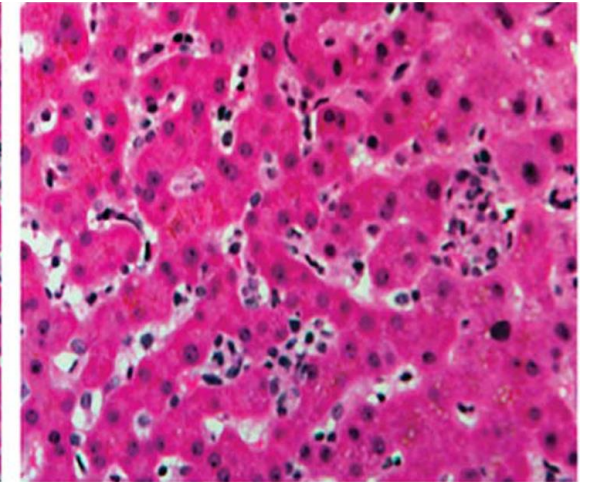
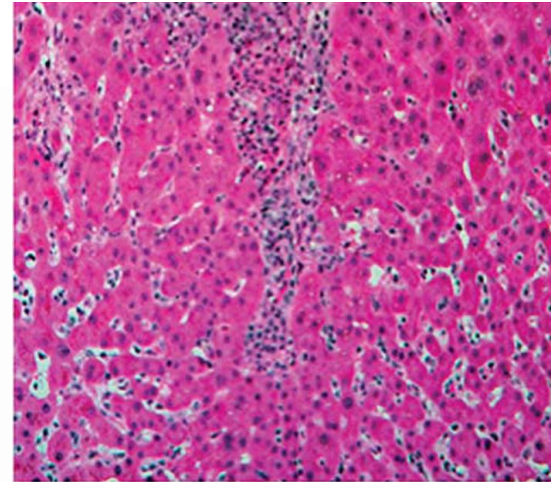
Model attention



Nieinwazyjna diagnostyka odrzucania po przeszczepieniu serca



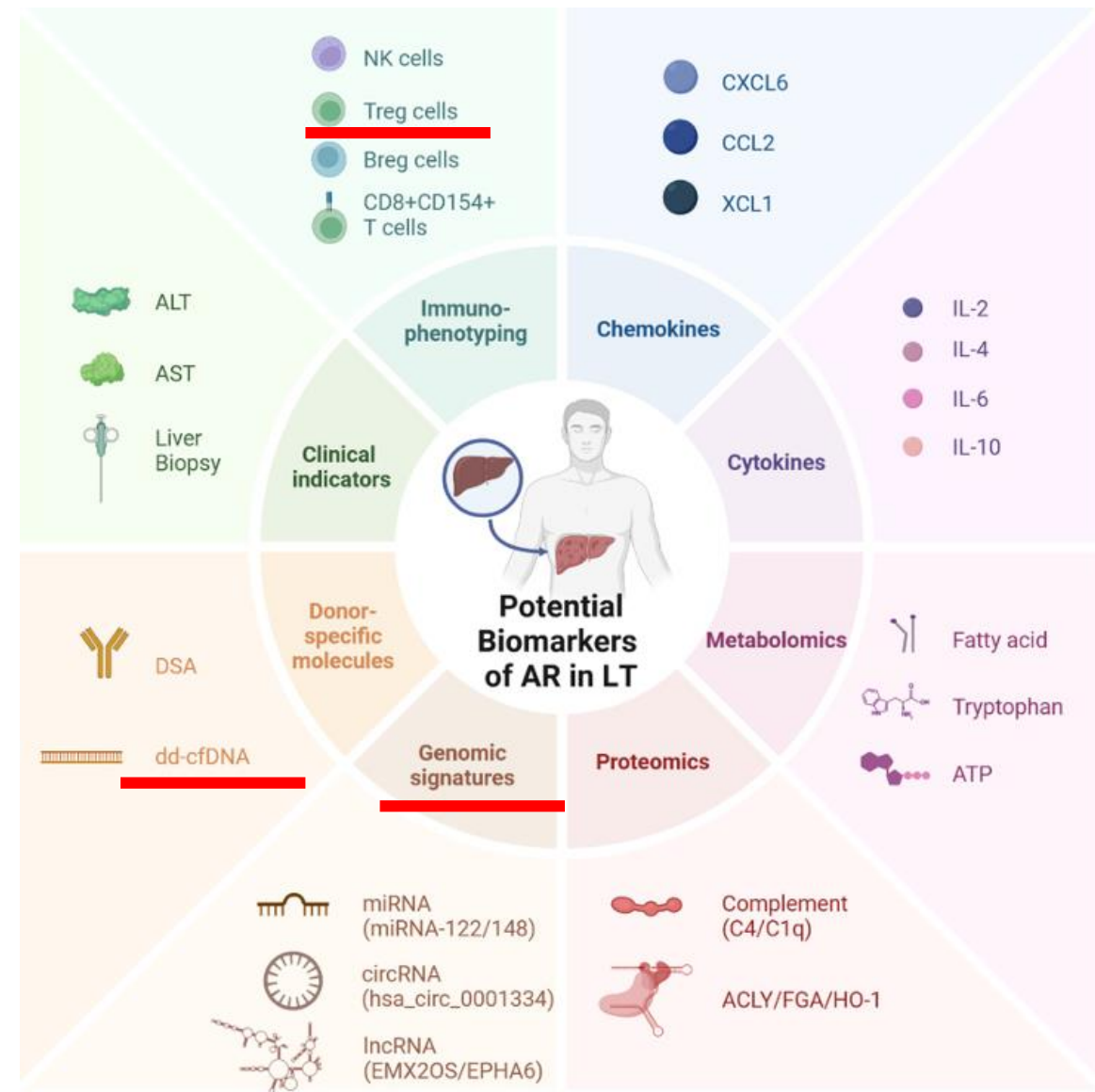
Biopsja cienko- lub gruboigłowa – standard w diagnostyce odrzucania



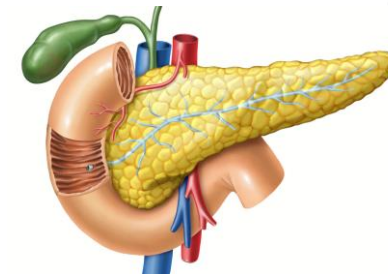
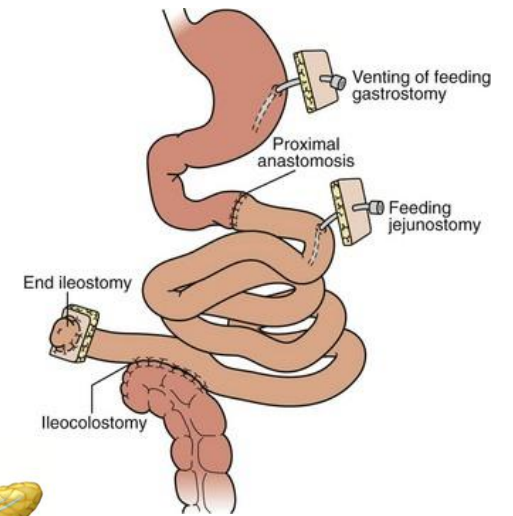
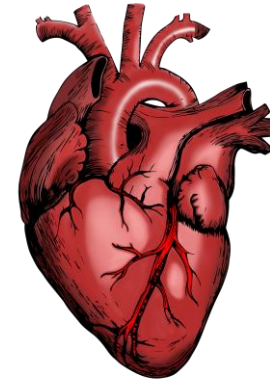
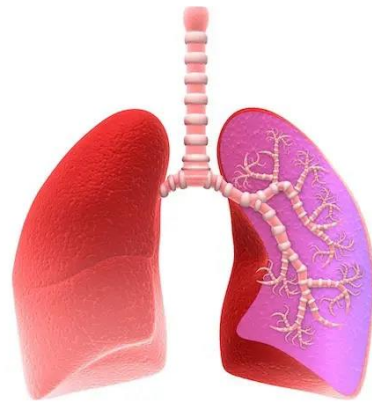
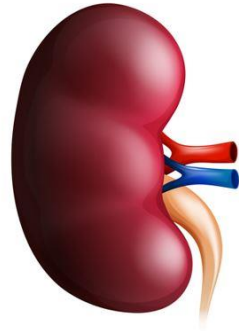
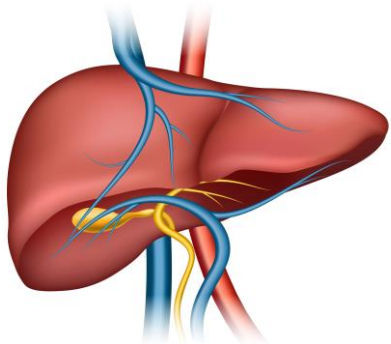
Nieinwazyjna diagnostyka odrzucania po przeszczepieniu wątroby

Representative biomarkers in predicting acute rejection after liver transplantation

Type	Biomarker	PPV	NPV	Reference
Donor-specific biomarkers	dd-cfDNA	66.7%	87.8%	39
	DSAs	NA	NA	49
Multi-omics data	36 gene panel	47%	87%	53
	59 gene panel	54%	89%	54
	3 miRNA panel	75%	93%	62
	470 proteoform panel	NA	NA	67
	C4, C1q	74%	94%	69
Cytokines and chemokines	ATP	NA	NA	74
	IL-6	NA	NA	78
	CCL2	NA	NA	82
Immunophenotyping	KIR ⁺ NK cells	NA	NA	90
	CD4 ⁺ CD25 ^{high} Tregs	58%	95%	92
	CD154 ⁺ T cells	64%	92%	95
	GZMB ⁺ CD19 ⁺ B cells	NA	NA	101



Immunogenność tkanek warunkuje ryzyko odrzucania i siłę immunosupresji



Leczenie immunosupresyjne