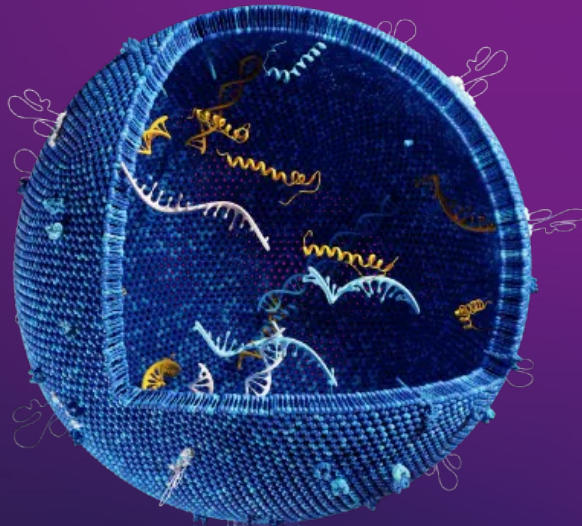




Toward Liquid Biopsy in Kidney Transplantation

J. Roumanos Azzi MD PhD

John P. Merrill, MD, and Charles B. Carpenter, MD, Endowed Chair in Transplantation Medicine

Associate Professor of Medicine, Harvard Medical School

Director, Transplantation Research Center

Director, Kidney and Pancreas Transplant Program

Brigham and Women's Hospital

Mass General Brigham

Jamil R. Azzi, MD PhD
Associate Professor of Medicine, Harvard Medical School

I have financial relationship(s) with:

- **Intellectual Properties:** ExosomeDx (Biotechne-Brand), Accrue inc., Lybra Bio, ImmuNanoDx.
- **Royalties:** Accrue inc., Lybra Bio
- **Founder:** Lybra Bio, ImmuNanoDx
- **Grants:** ExosomeDx (Biotechne-Brand), CareDx, Moderna Inc., Alexion, Thermo Fisher
- **Consultancy:** Moderna Inc., Trustech, Kezar Life Sciences, Chinook Therapeutics
- **Advisory Boards:** Trustech, CareDx, Moderna Inc., Vertex, Alexion

AND

My presentation does include discussion of off-label or investigational use.

More than meets the eye

19 yo male with history of ESRD secondary to congenital kidney disease
S/P deceased kidney transplant 1/24/26 (KDPI 46%), 4 HLA MM, PRA 0%
induced with Thymo.

Had multiple GI symptoms and had Mycophenolic Acid switched to
Imuran and dose reduced due to leukopenia and EBV viremia detected
in a high-risk patient.

Creatinine plateaued around 2.

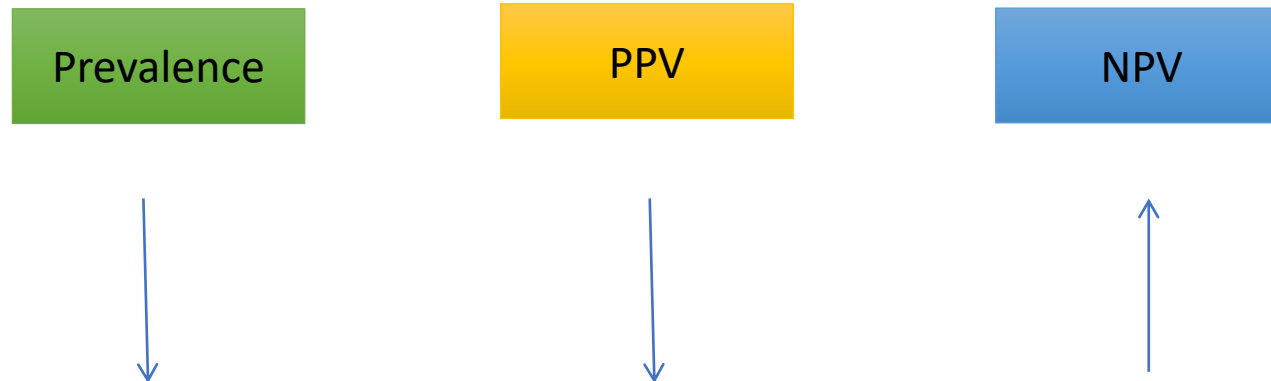
Biopsy done 4/6: No rejection

Creatinine worsened

Biopsy done 4/28: ACR and AMR with de novo DSA.

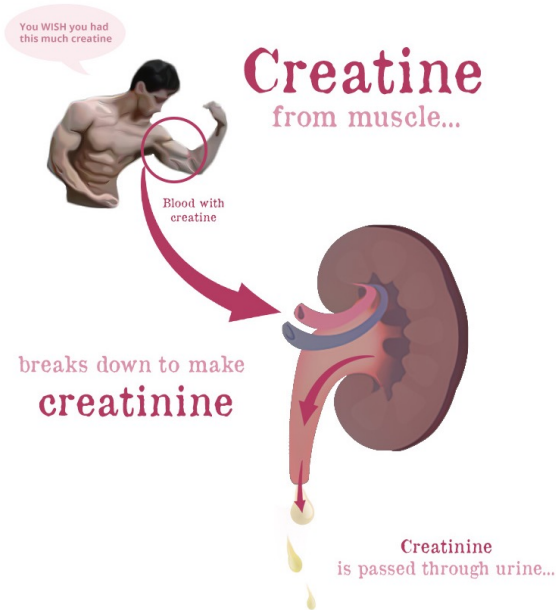
Impact of Prevalence on predictive values

- Positive predictive value (PPV) is the number of true positives if the test is positive
- Negative predictive value (NPV) is the number of true negatives if the test is negative

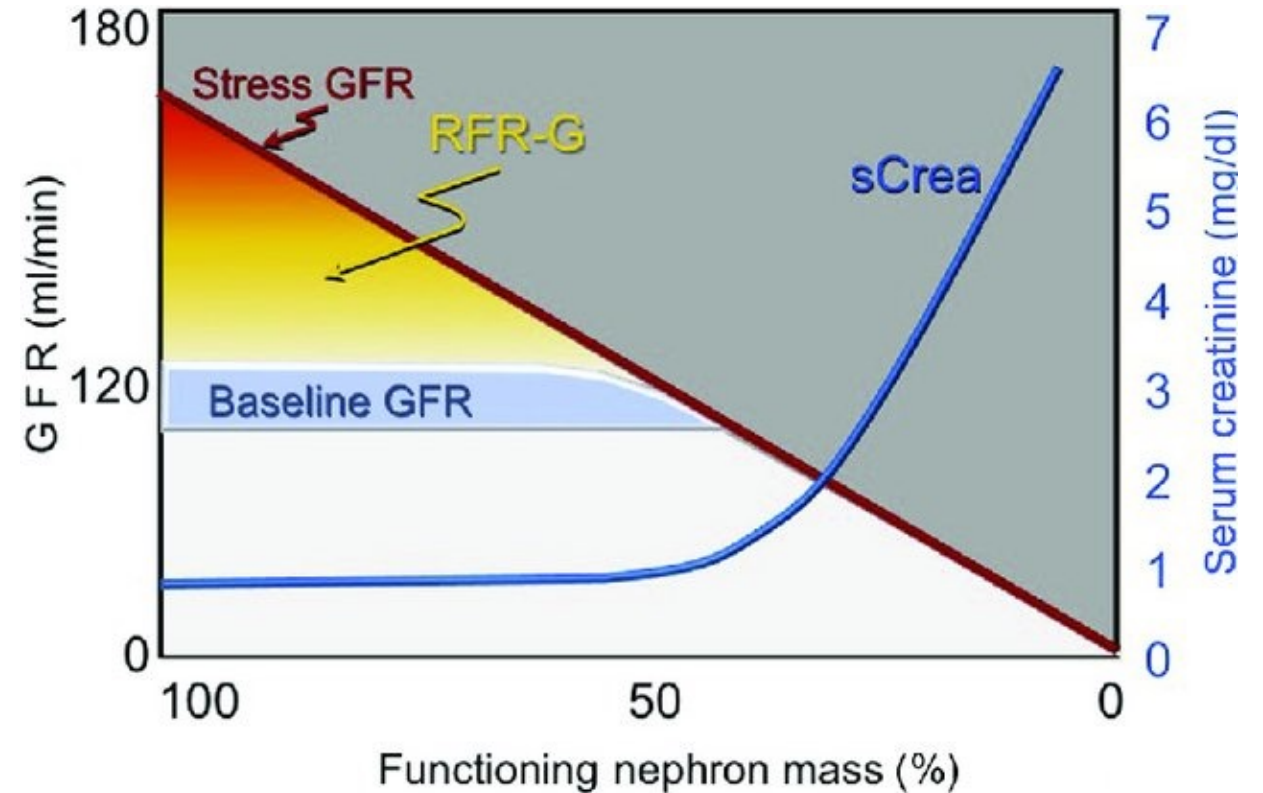


Monitoring kidney function through serum creatinine: The Last To Know

WHERE DOES CREATININE
COME FROM?



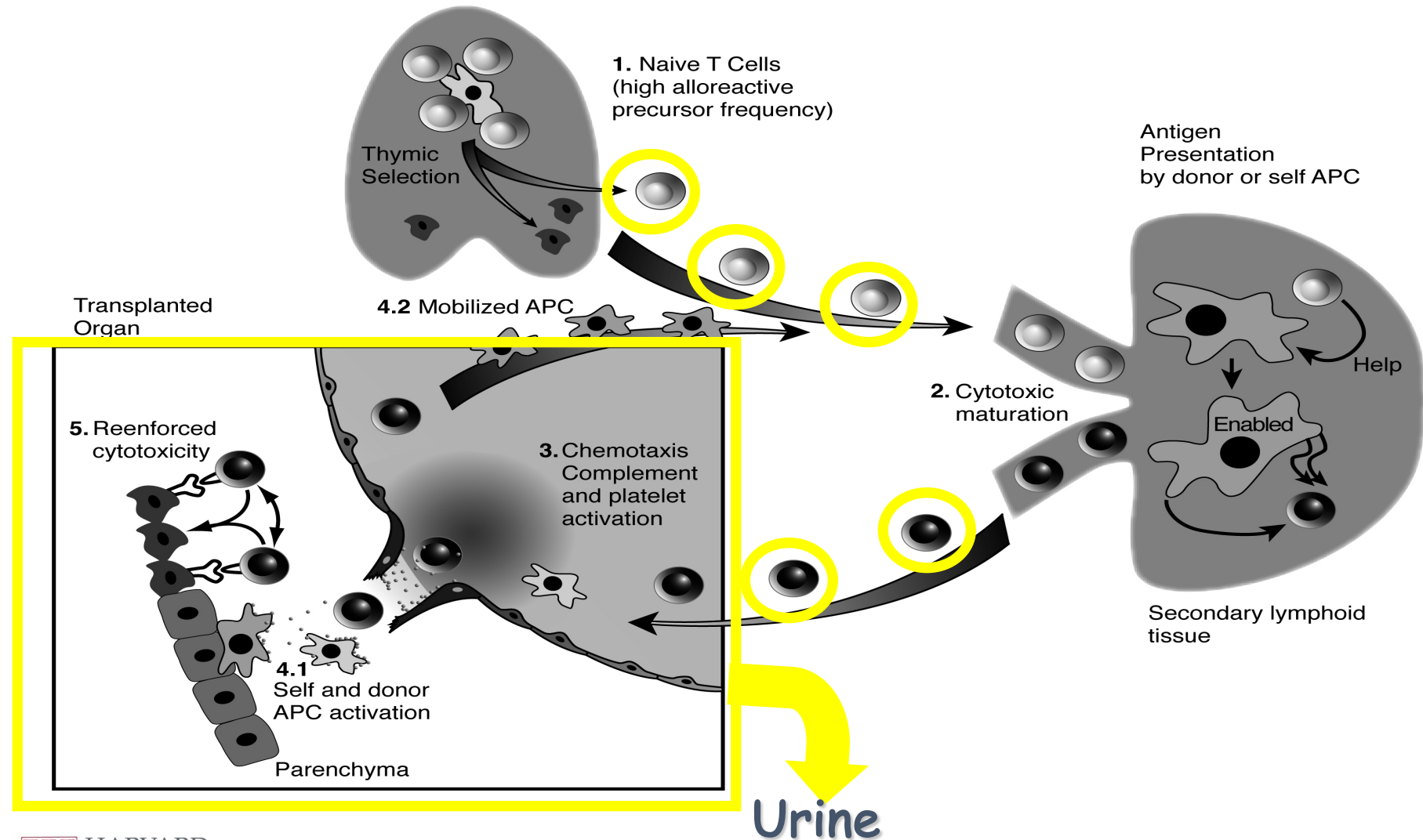
But in kidney failure,
your blood creatinine level will go up.



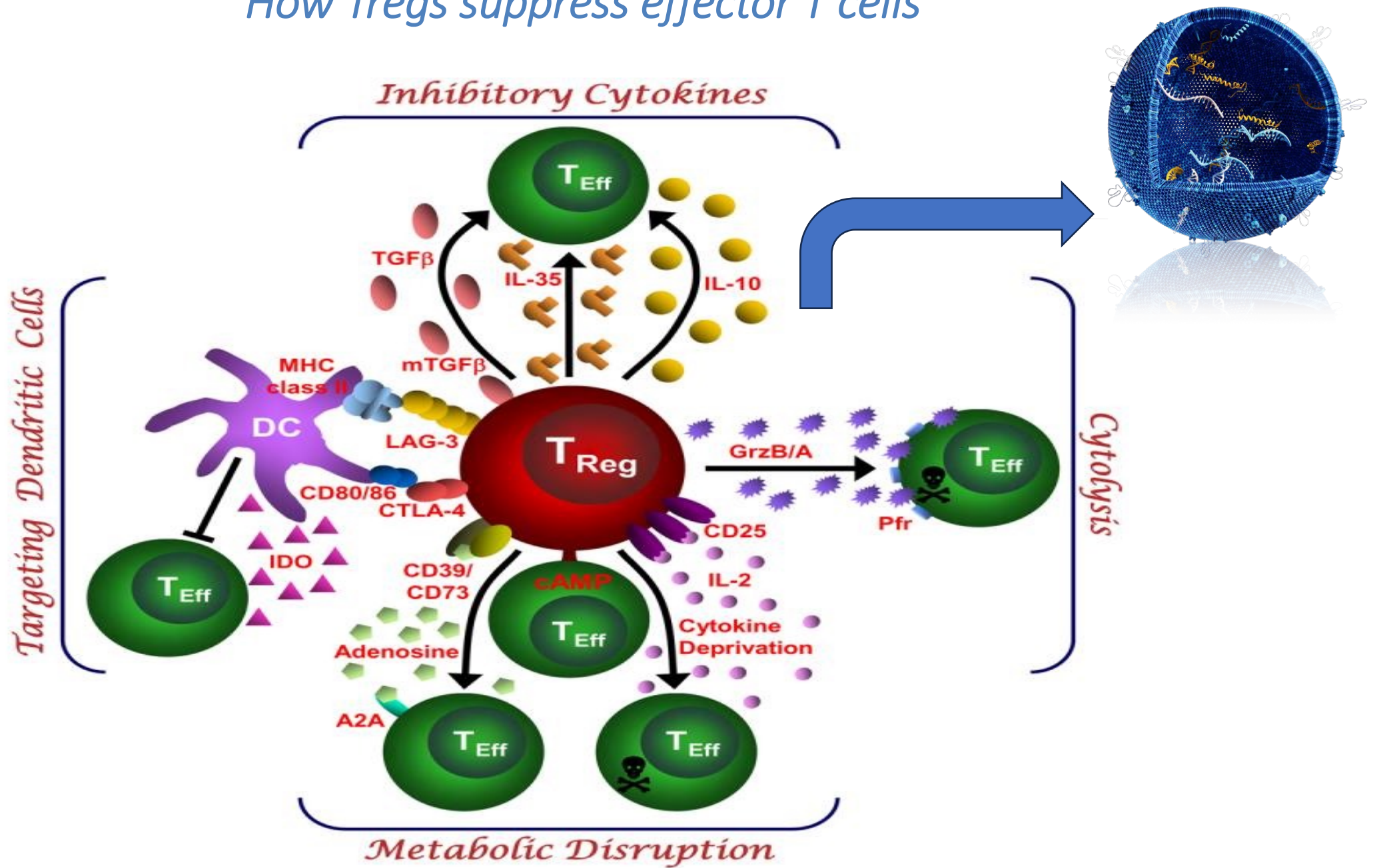
20 % Subclinical rejection

Mechanisms of Immune Monitoring

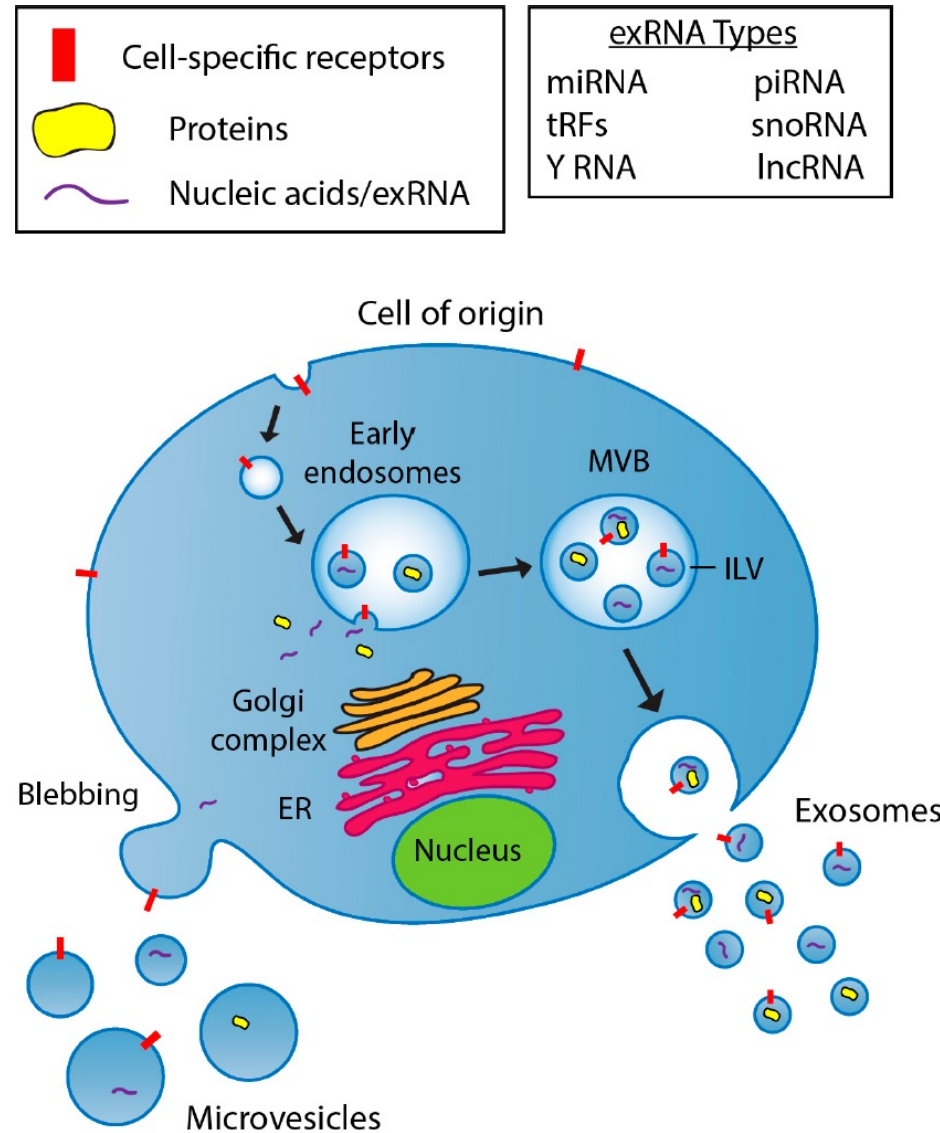
What's Available for Evaluation?



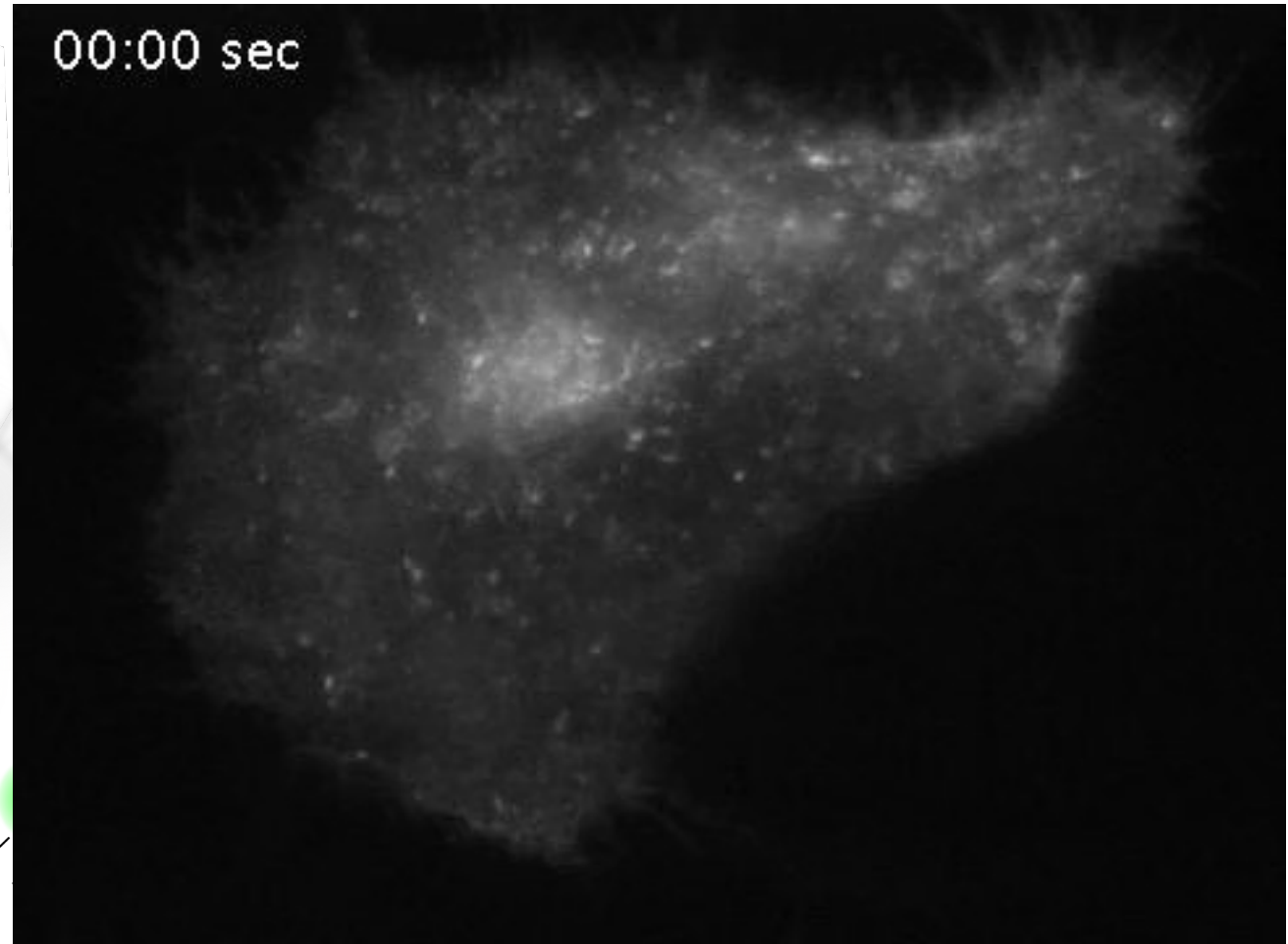
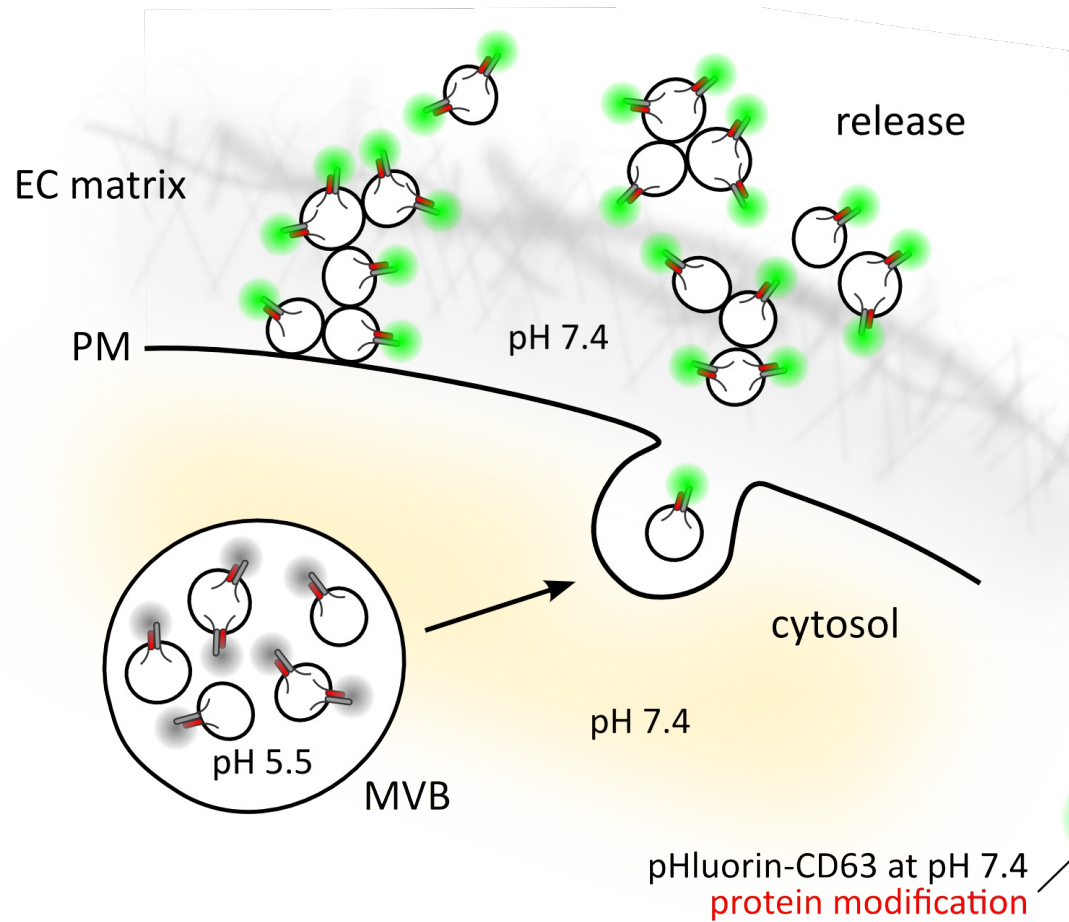
How Tregs suppress effector T cells



Extracellular vesicles

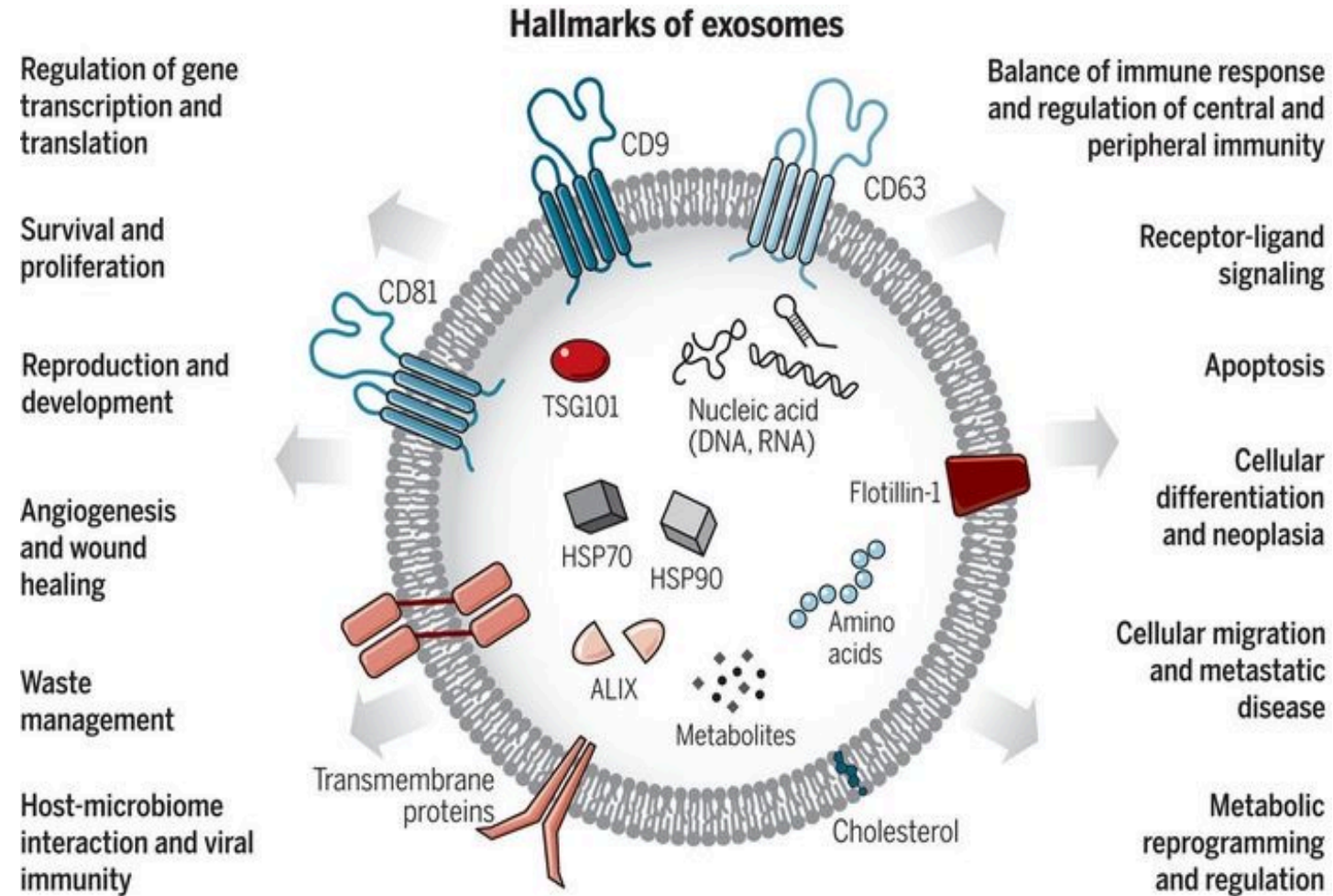


LIVE-IMAGING REVEALS EXOSOME SECRETION DYNAMICS FROM A SINGLE LIVING CANCER CELL



Verweij et al., J Cell Biol 2018

High Throughput approach of discovery



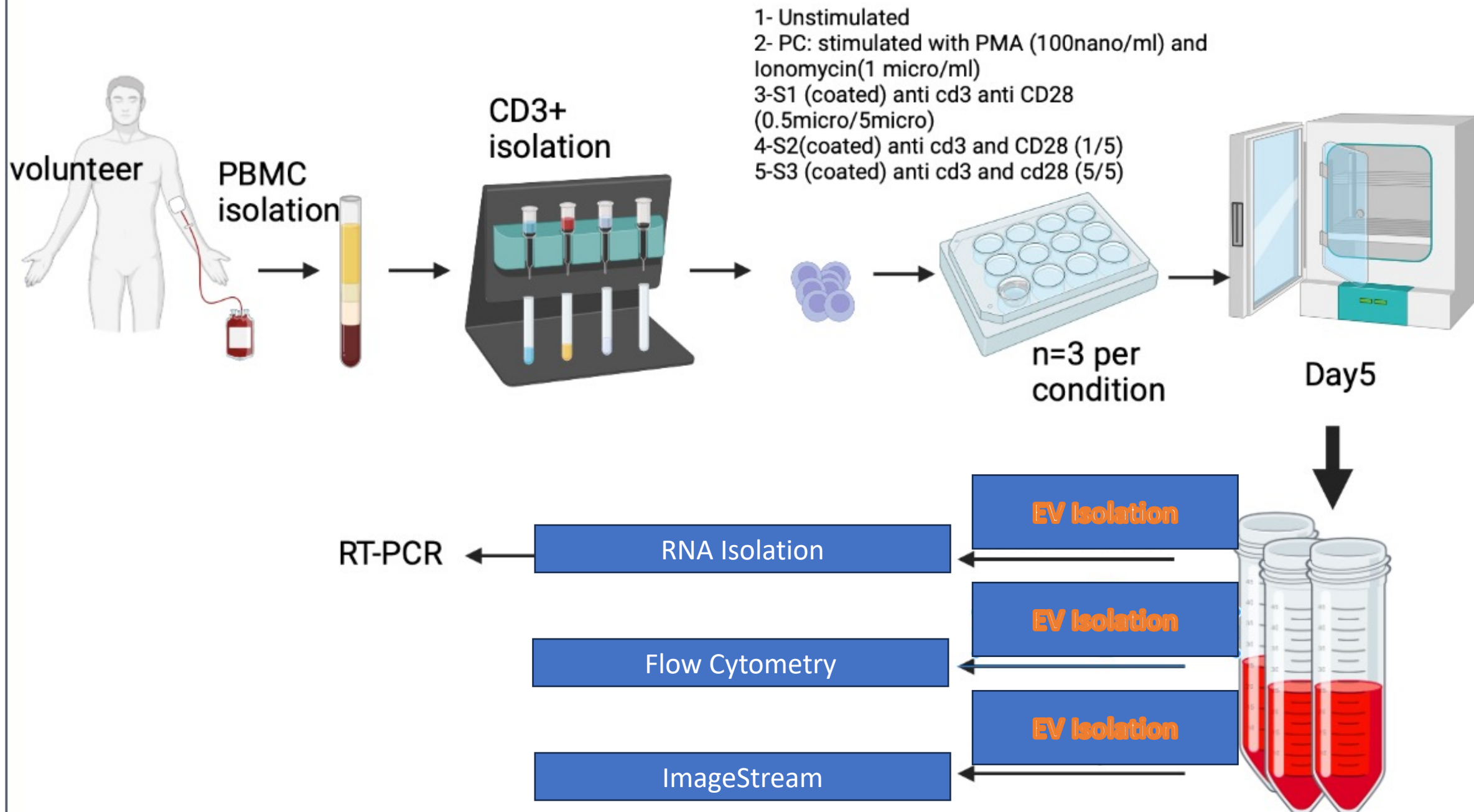
The biology, function, and biomedical applications of exosomes, Volume: 367, Issue: 6478, DOI: [10.1126/science.aau6977](https://doi.org/10.1126/science.aau6977)

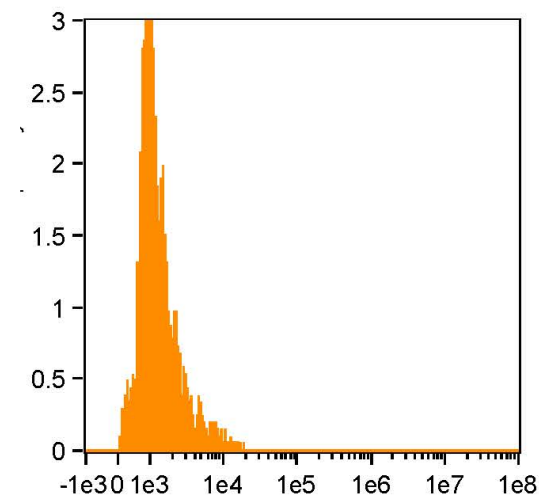
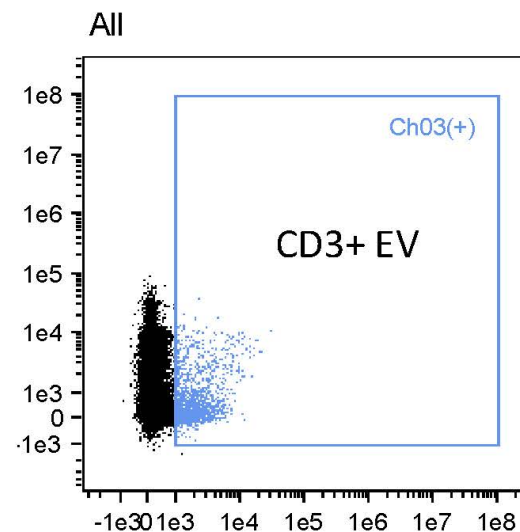
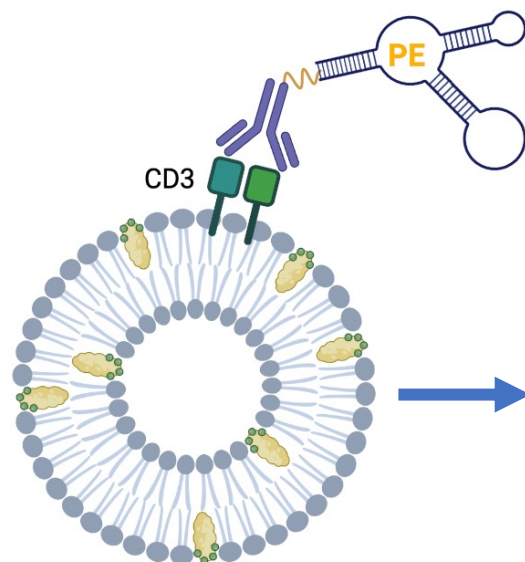


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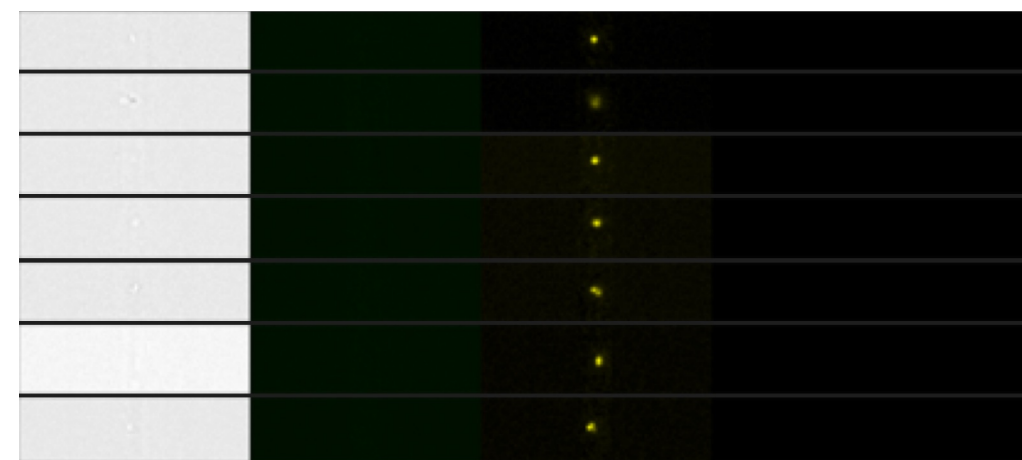


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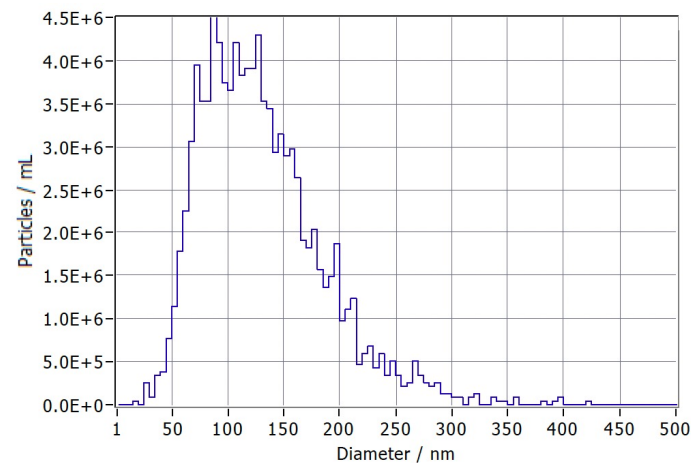
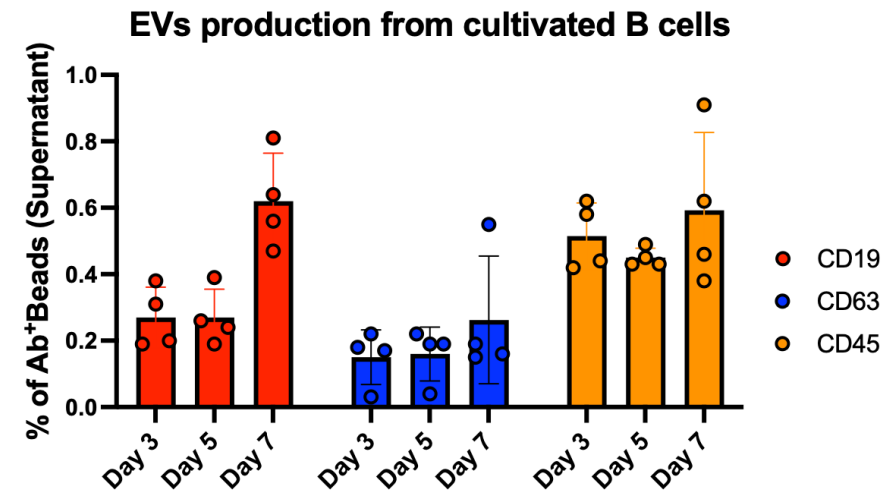
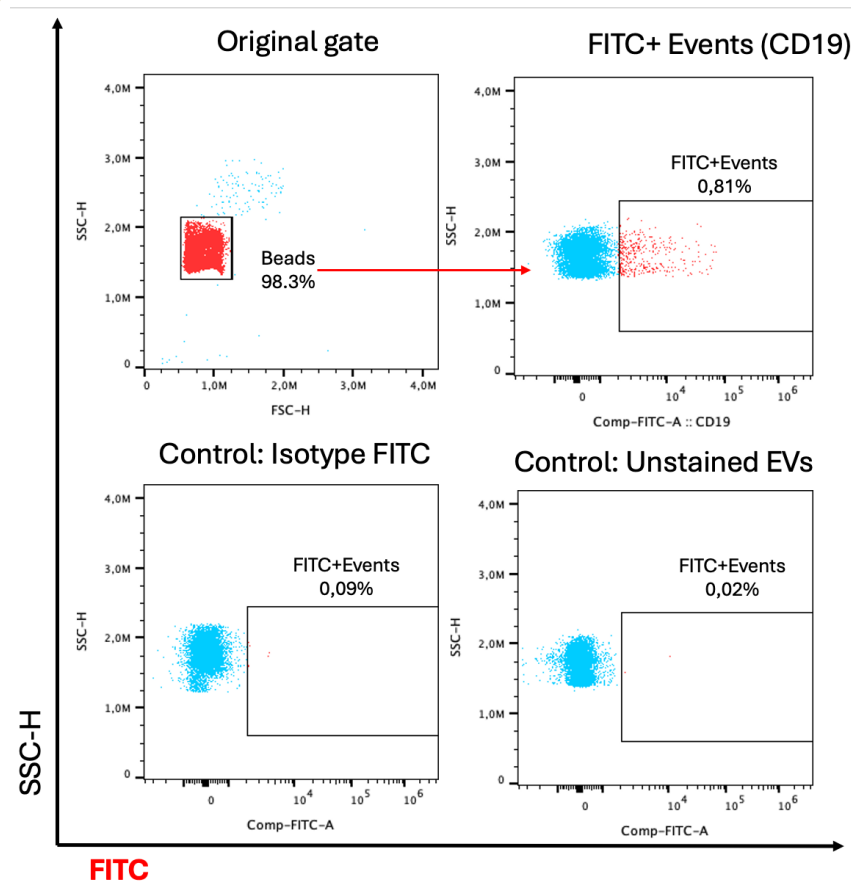




Single EV

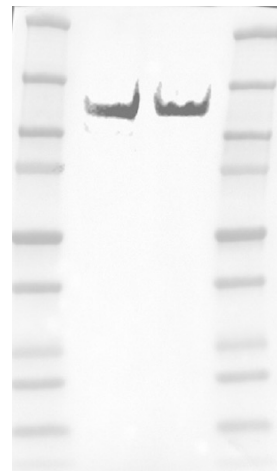


B cell specific EV

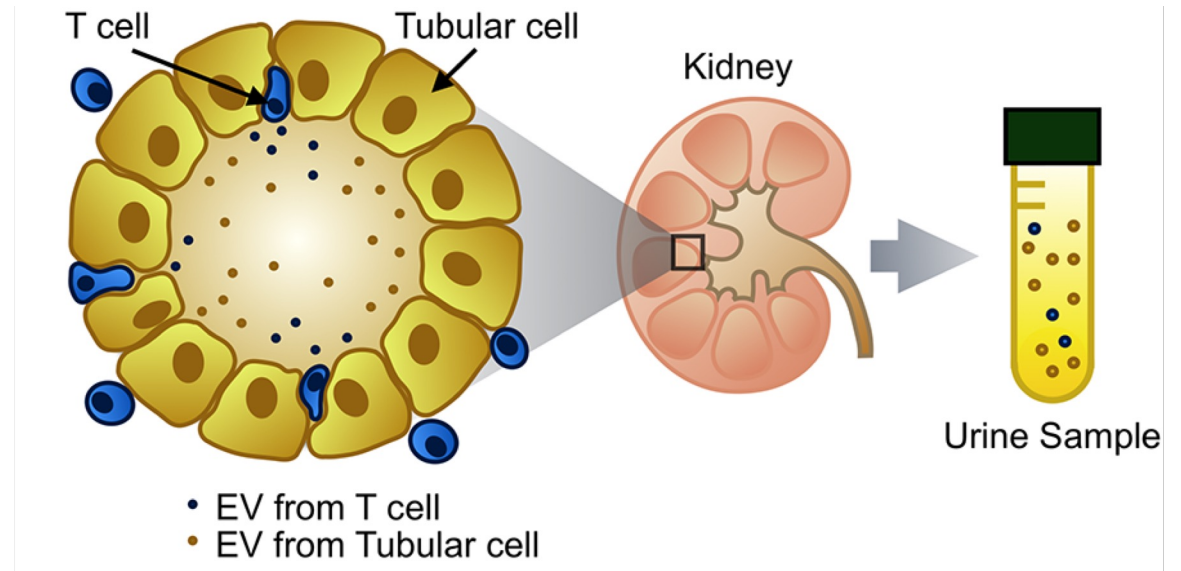
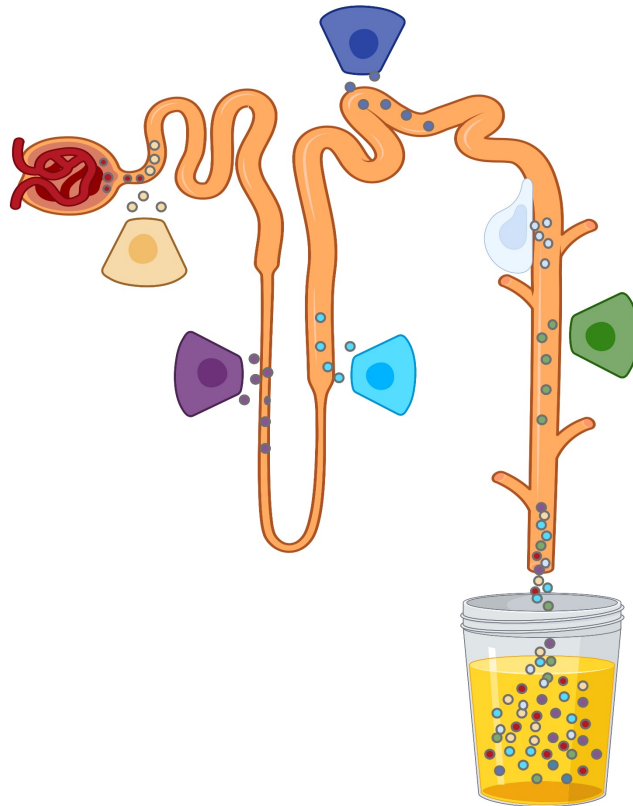


Mean diameter 119.4 ± 54.6 nm
 Concentration: 5.1×10^{10} particles/mL

CD45 150 kDa



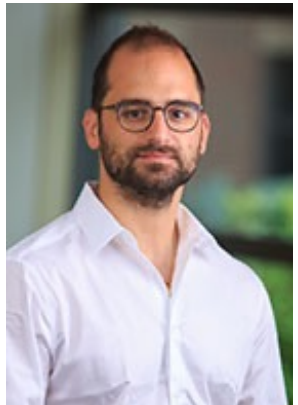
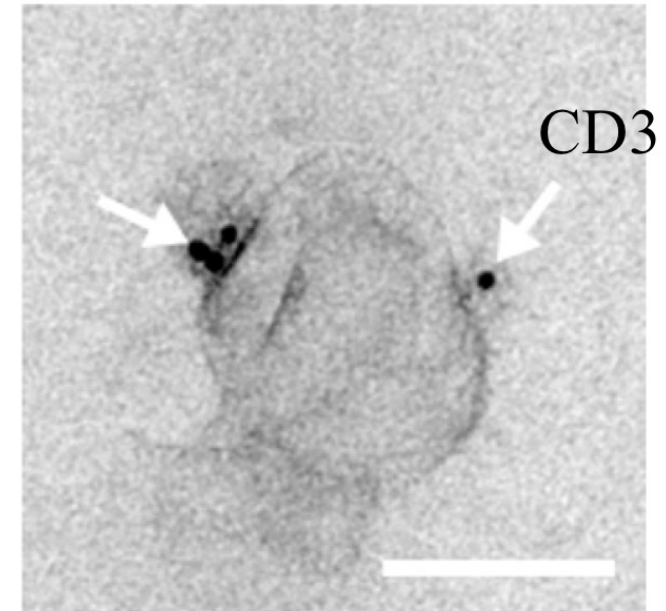
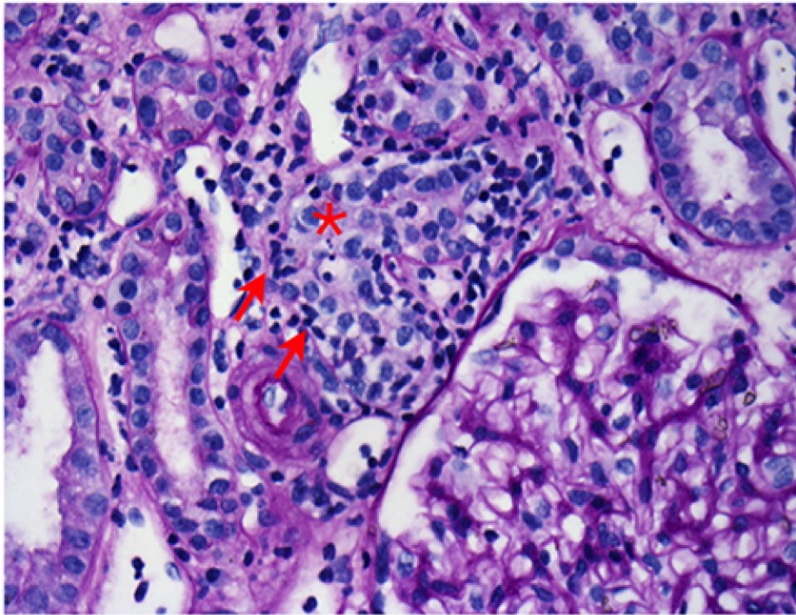
Immune cell specific EVs in urine of rejecting kidney allografts



Immune cell specific EVs in urine of rejecting kidney allografts



Jongmin Park



Jean Pierre Assaker



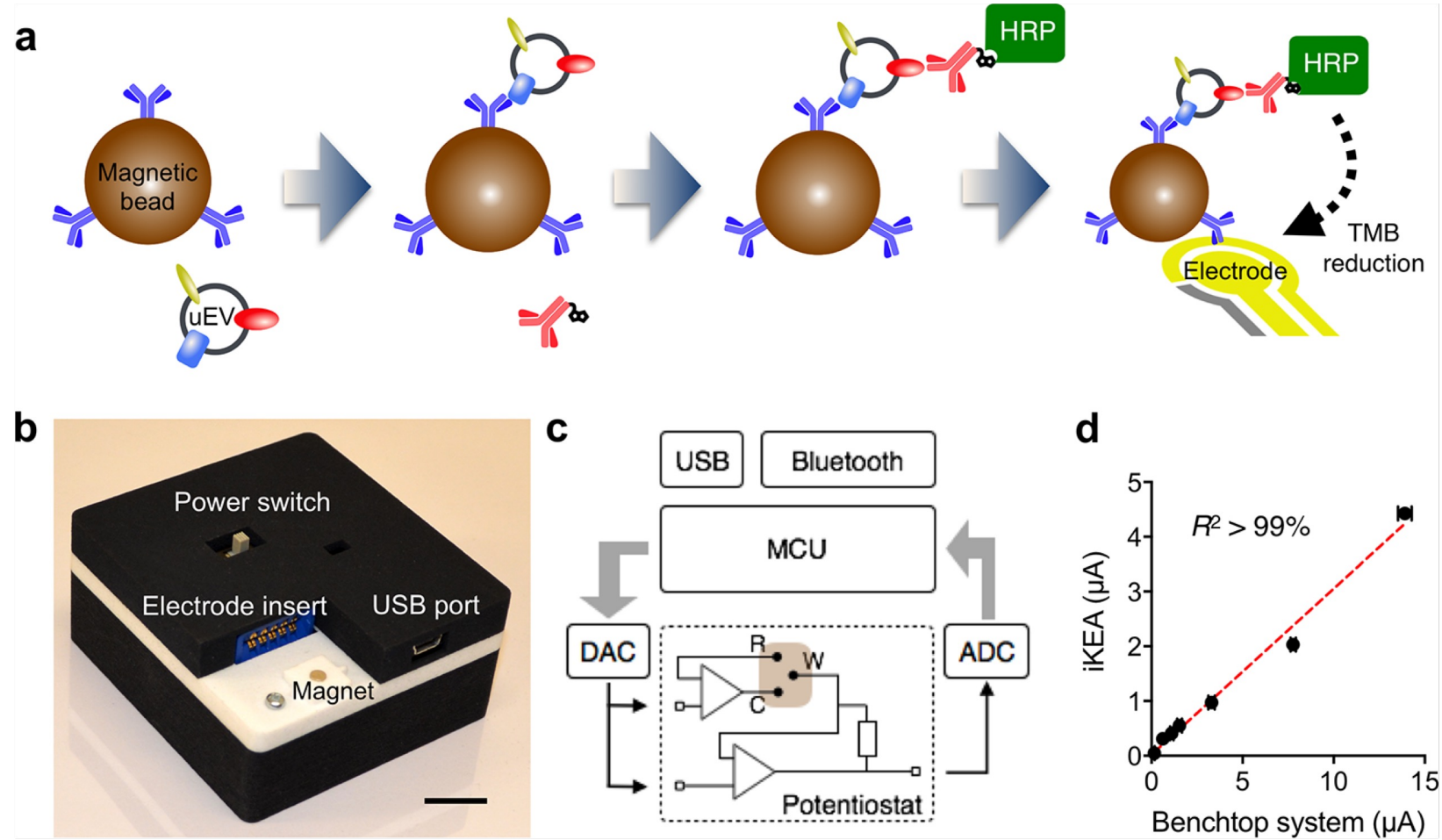
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Park...Lee and Azzi et al. ACS Nano. 2017 11 28; 11(11):11041-11046.

Integrated Kidney Exosome Analysis (iKEA)



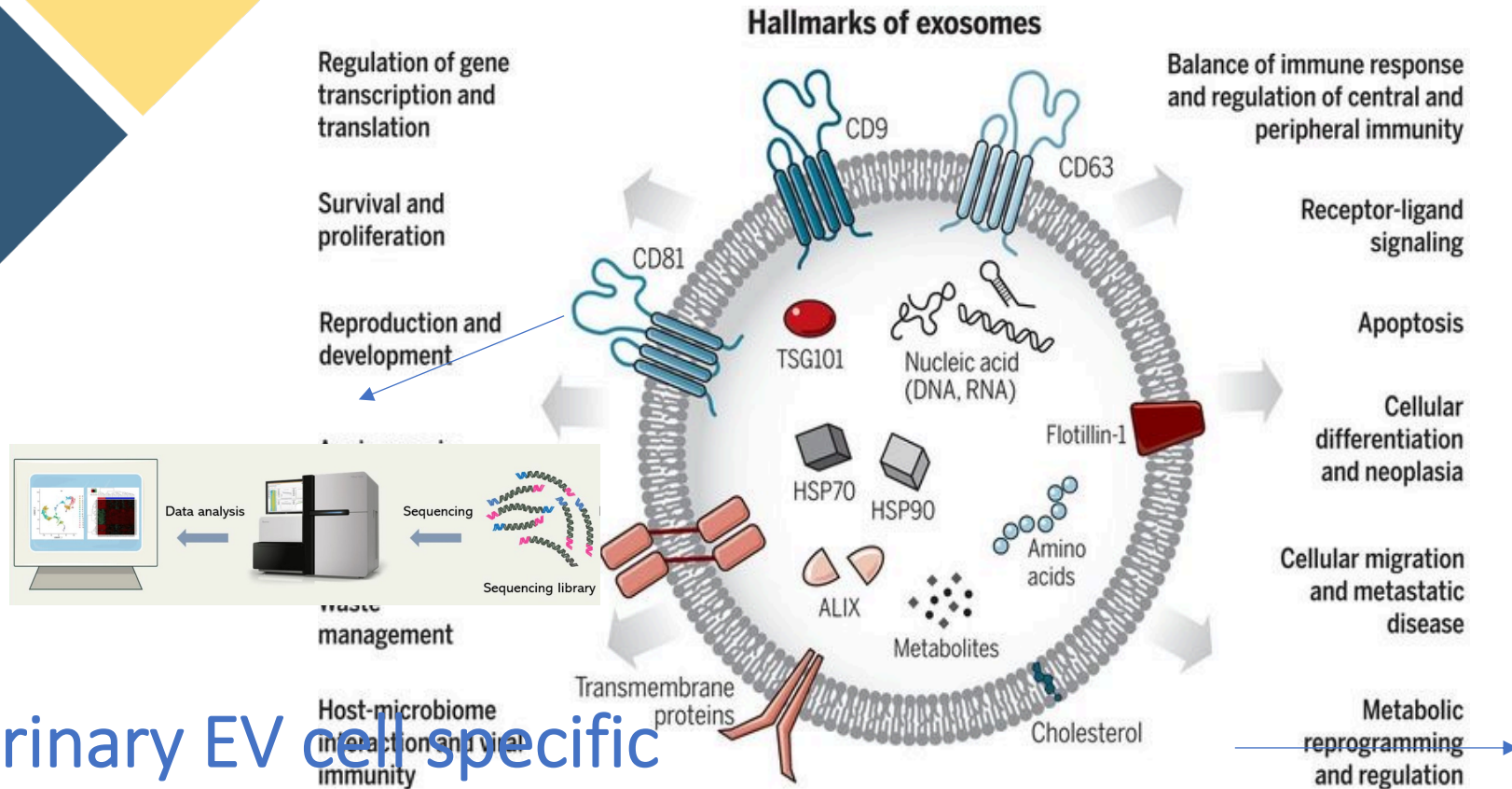


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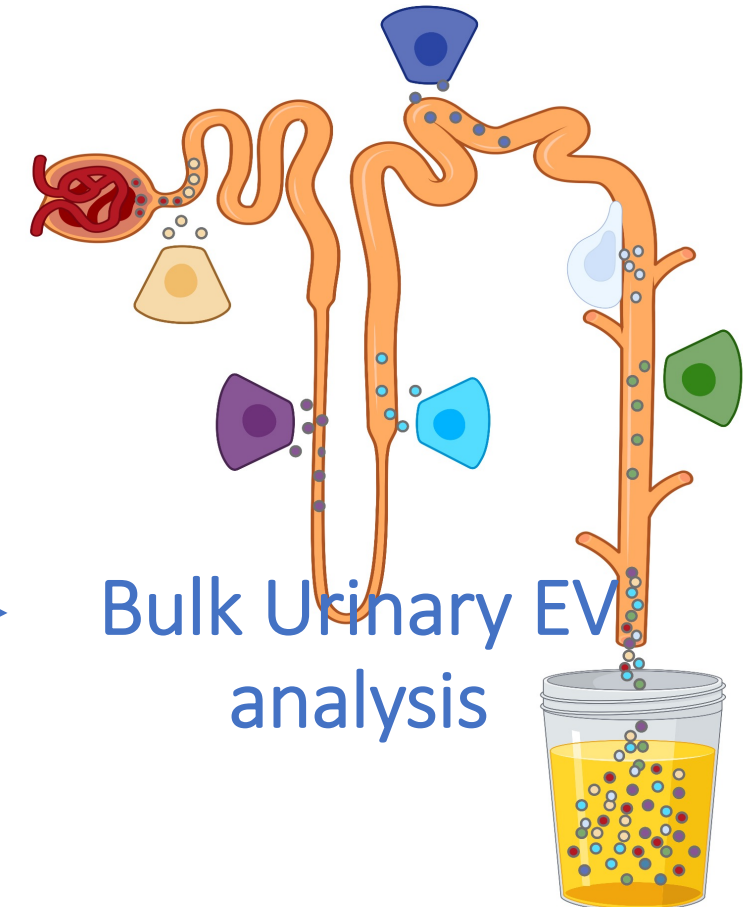
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High Throughput approach of discovery



Urinary EV cell specific signatures

The biology, function, and biomedical applications of exosomes, Volume: 367, Issue: 6478, DOI: (10.1126/science.aau6977)



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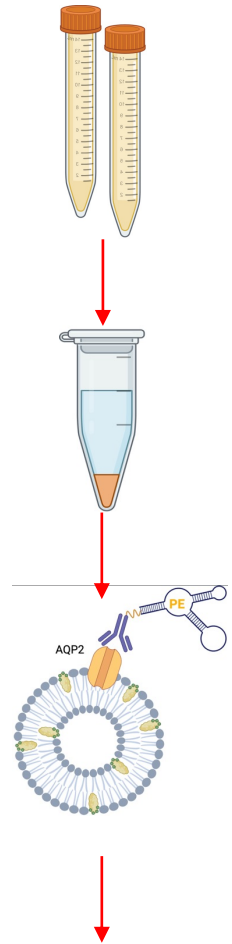
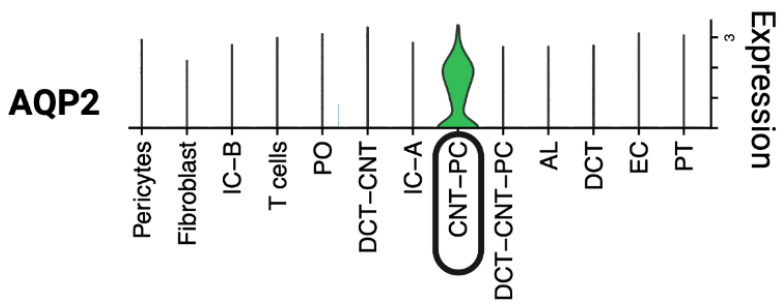
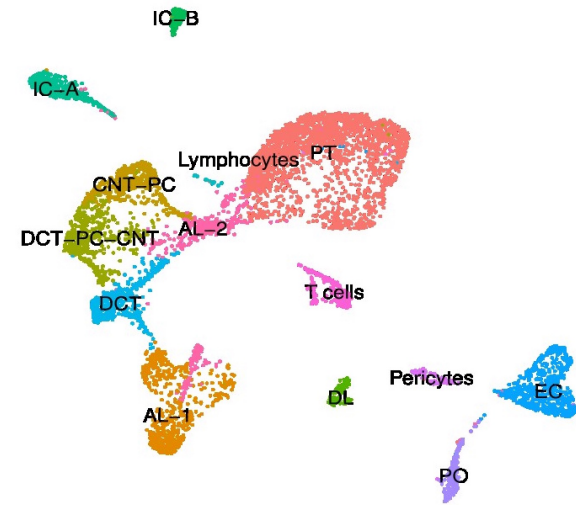
Cell specific EV signature



Surface Protein Specific for
Kidney Cells

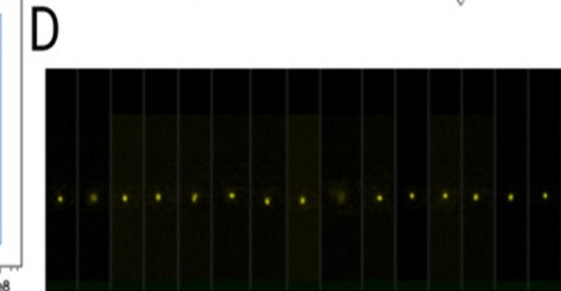
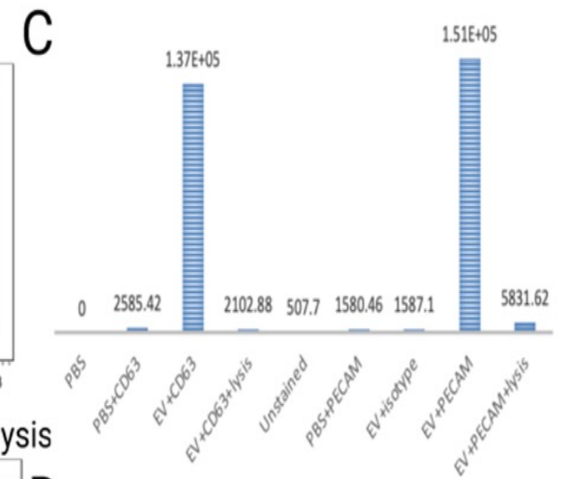
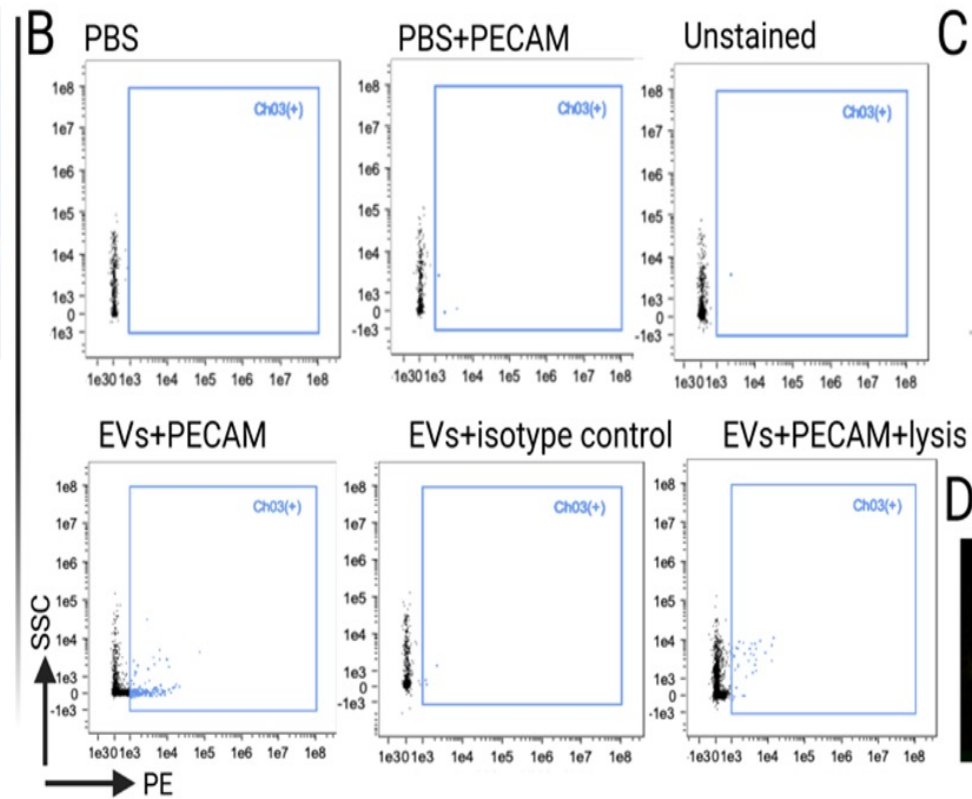
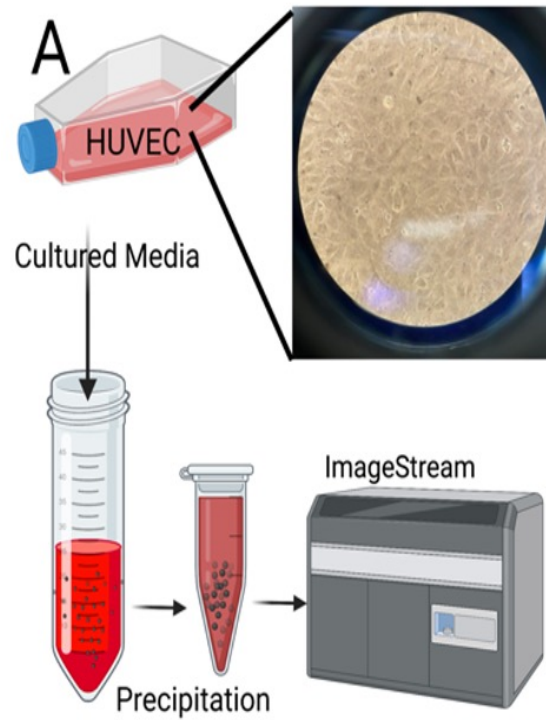
+

Present on EVs

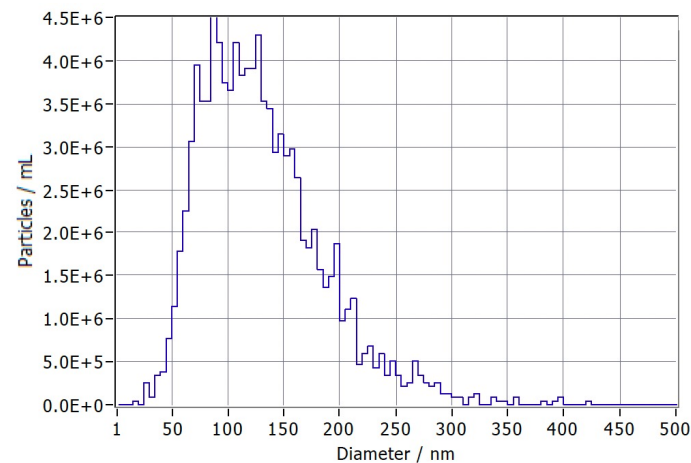
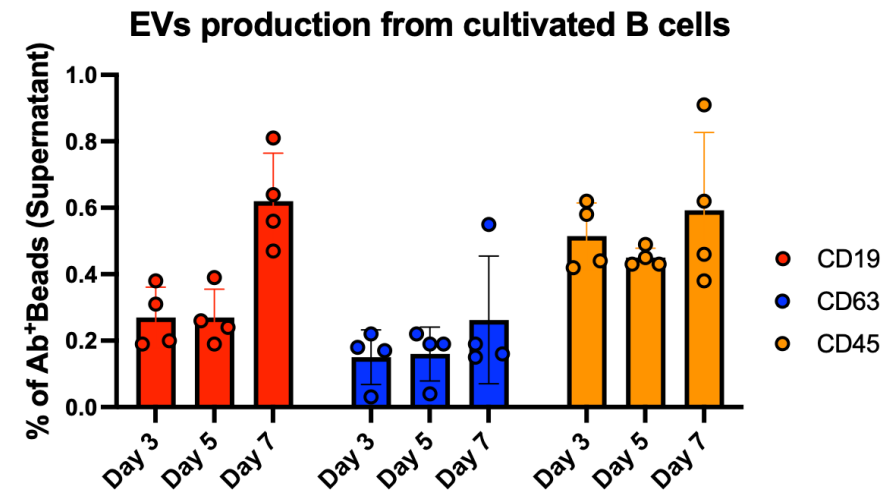
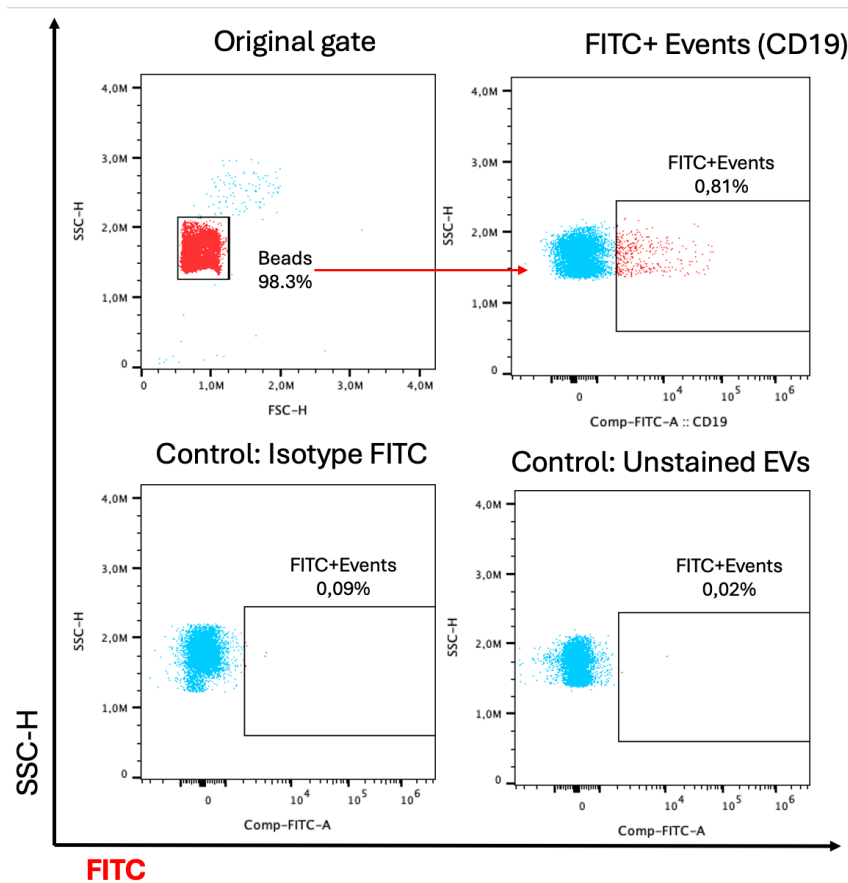


Unpublished data

Endothelial cell specific EV

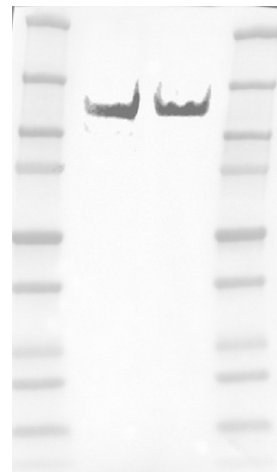


B cell specific EV

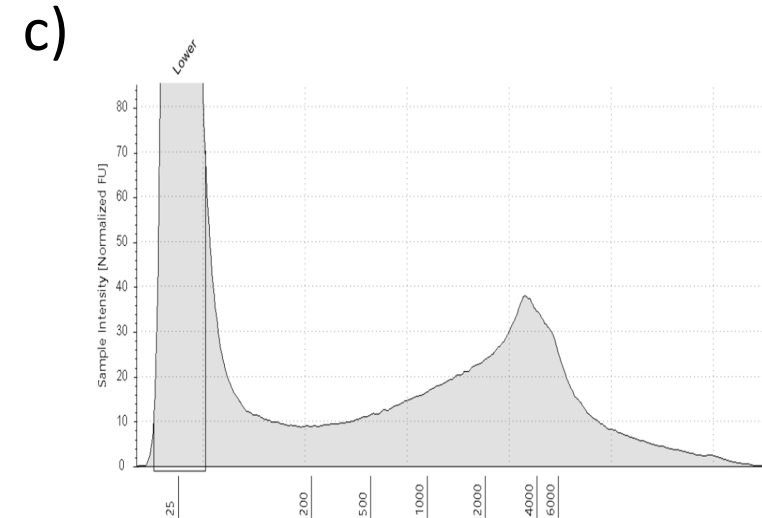
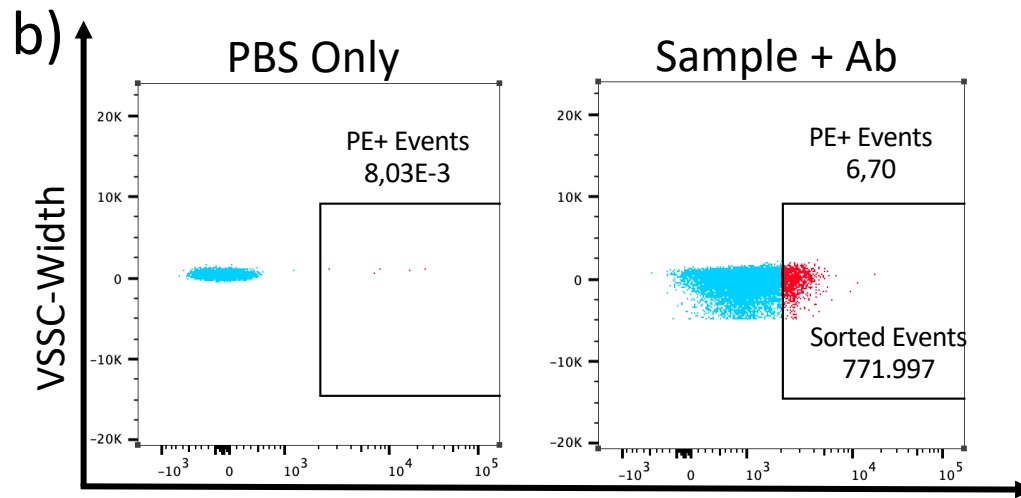
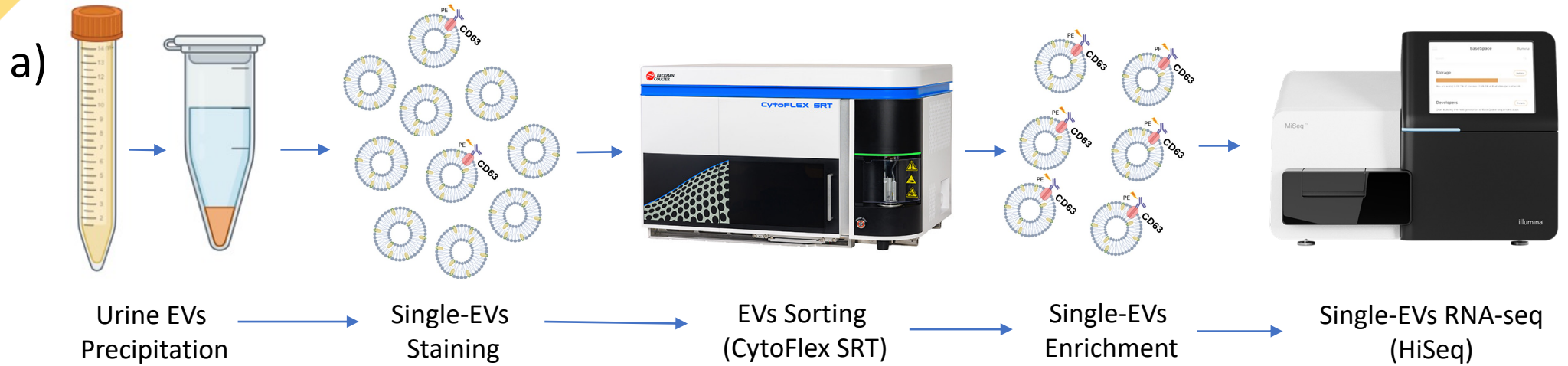


Mean diameter 119.4 ± 54.6 nm
 Concentration: 5.1×10^{10} particles/mL

CD45 150 kDa



EV sorting is possible

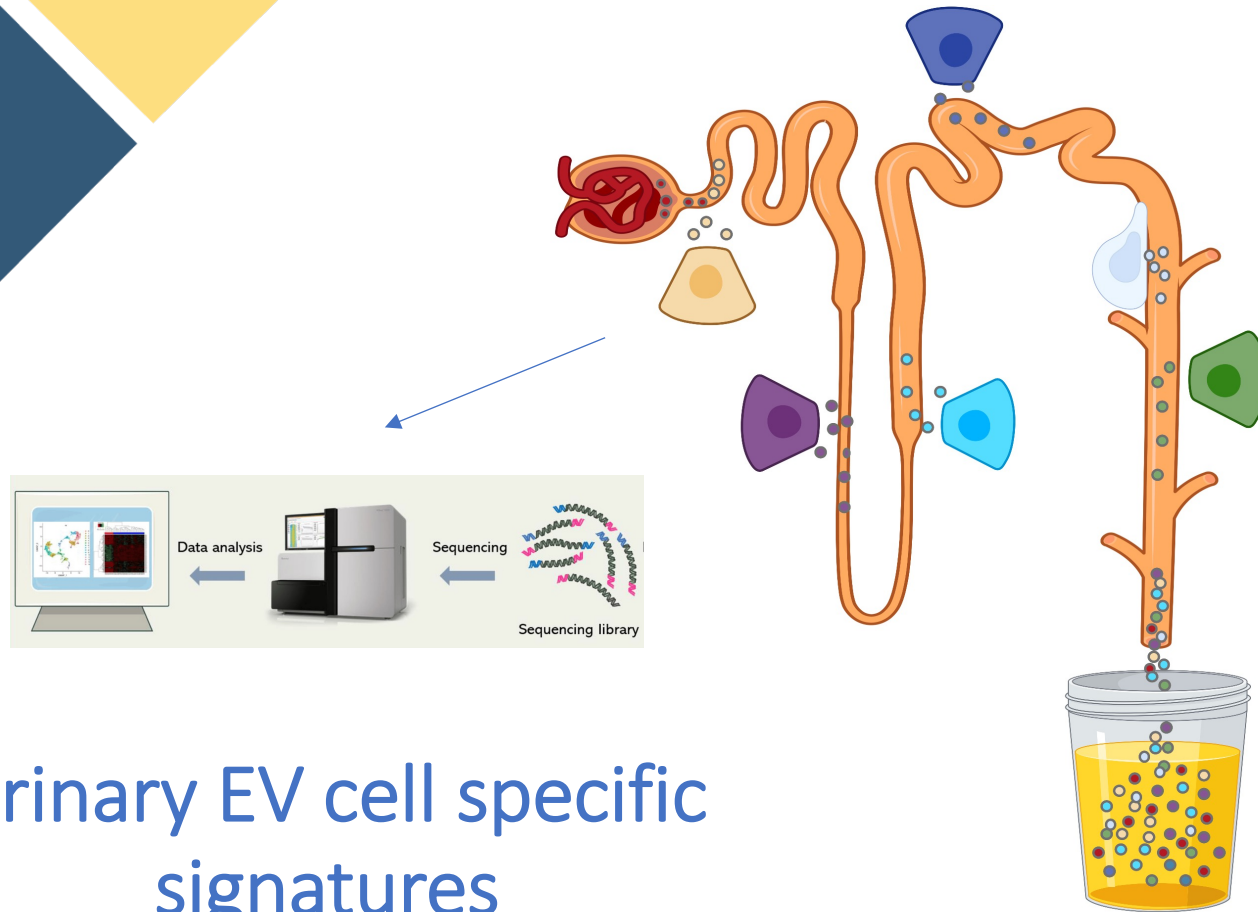


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High Throughput approach of discovery



Urinary EV cell specific
signatures

Bulk Urinary EV
analysis



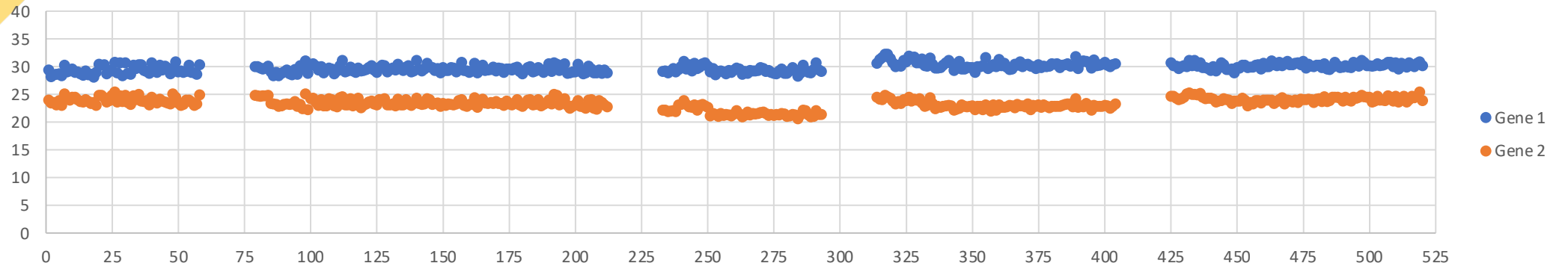
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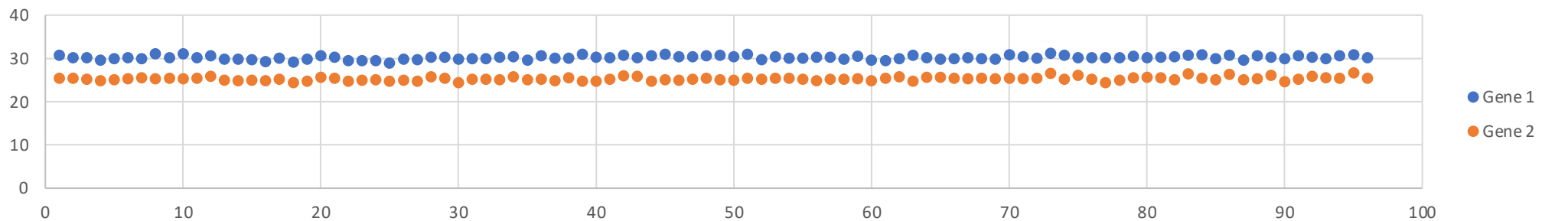
Urine exosome RNA stability

Reproducibility- Control Urine Batches



Extraction replicate

Batch 5 - Detail



Extraction replicate

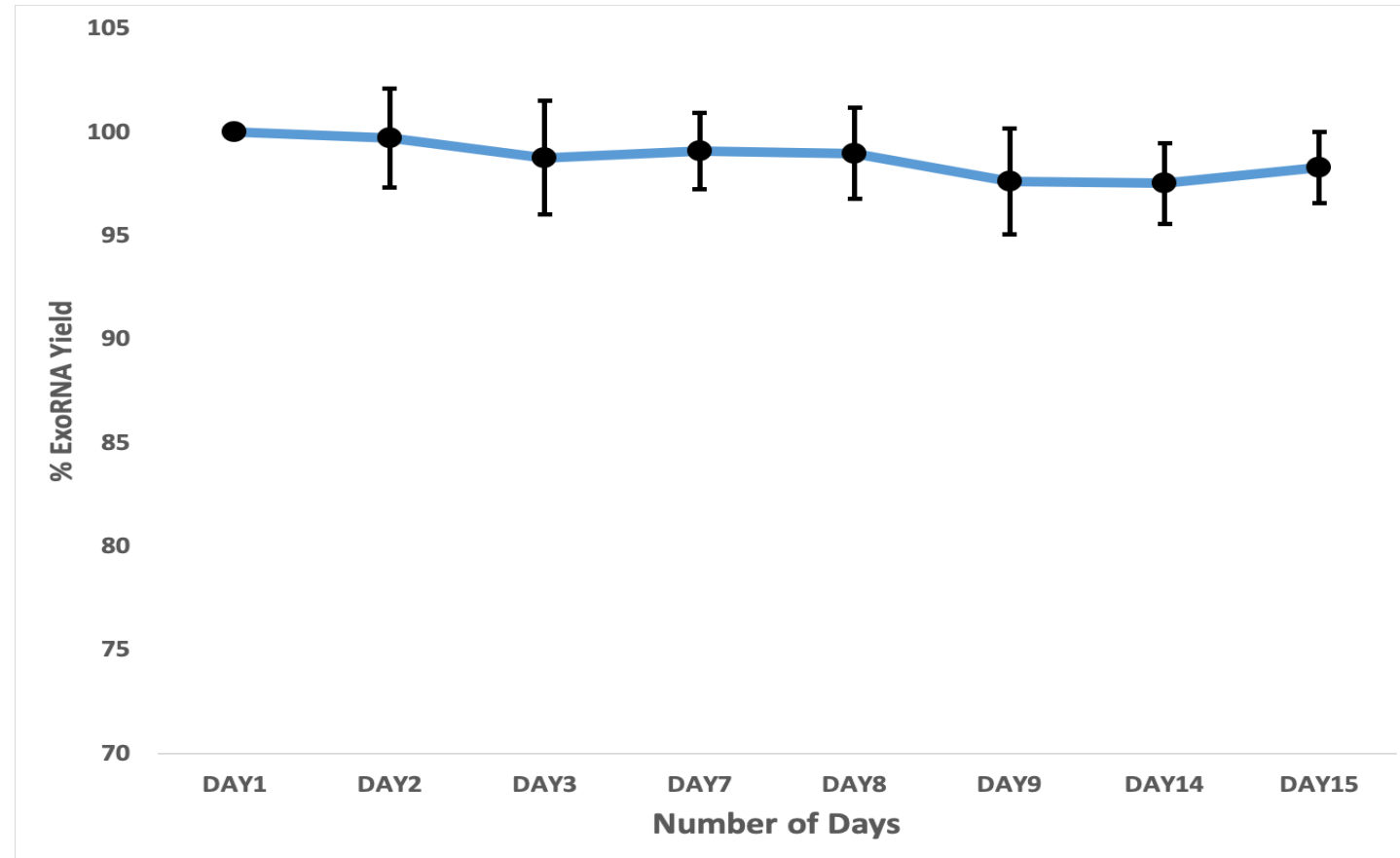


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Urine exosome RNA stability

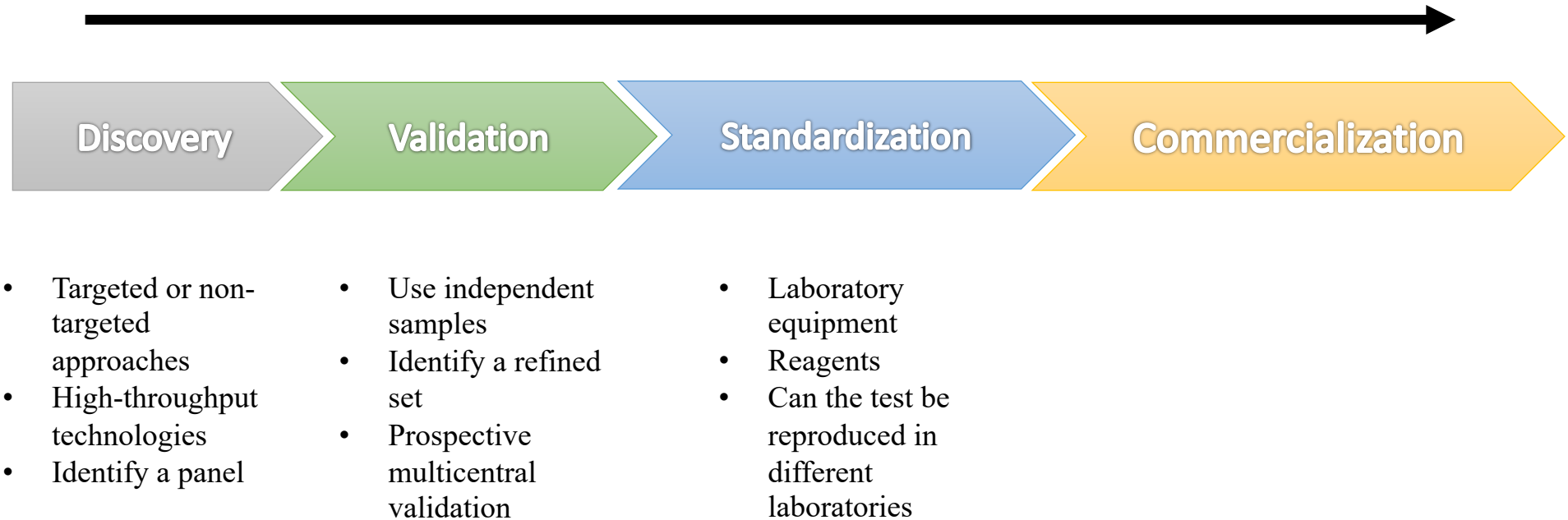


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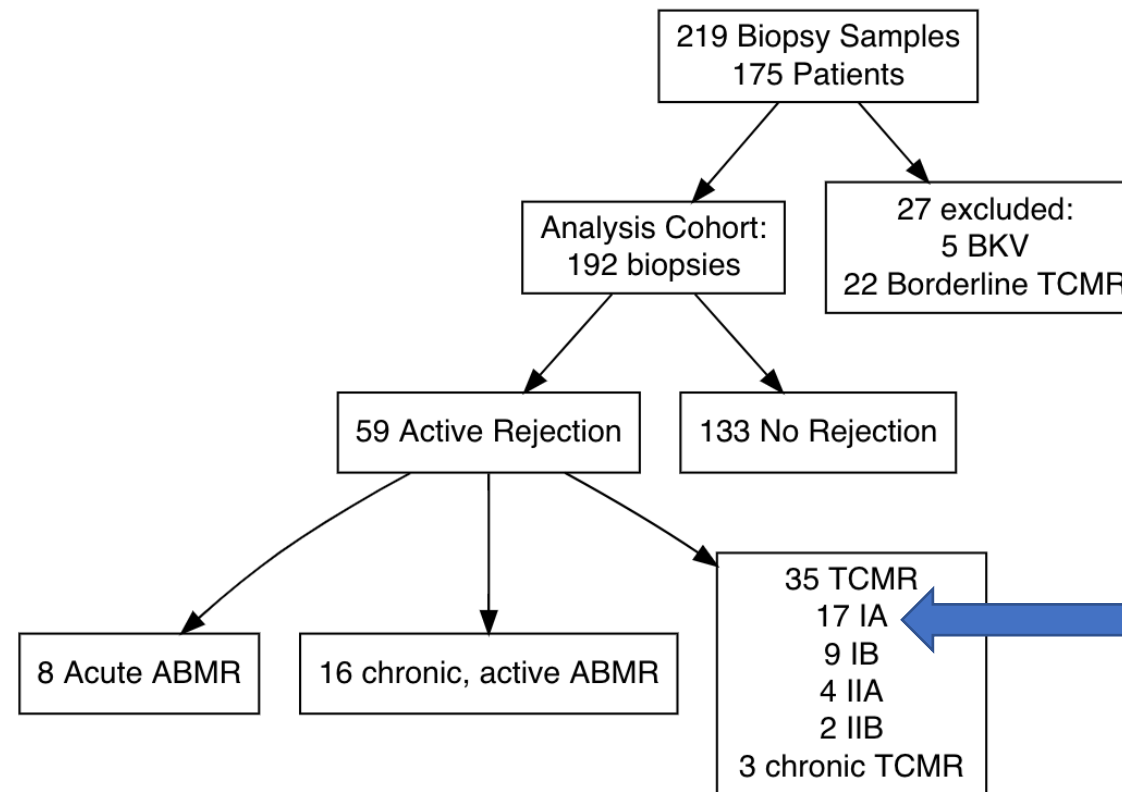
Phases of Biomarkers Discovery



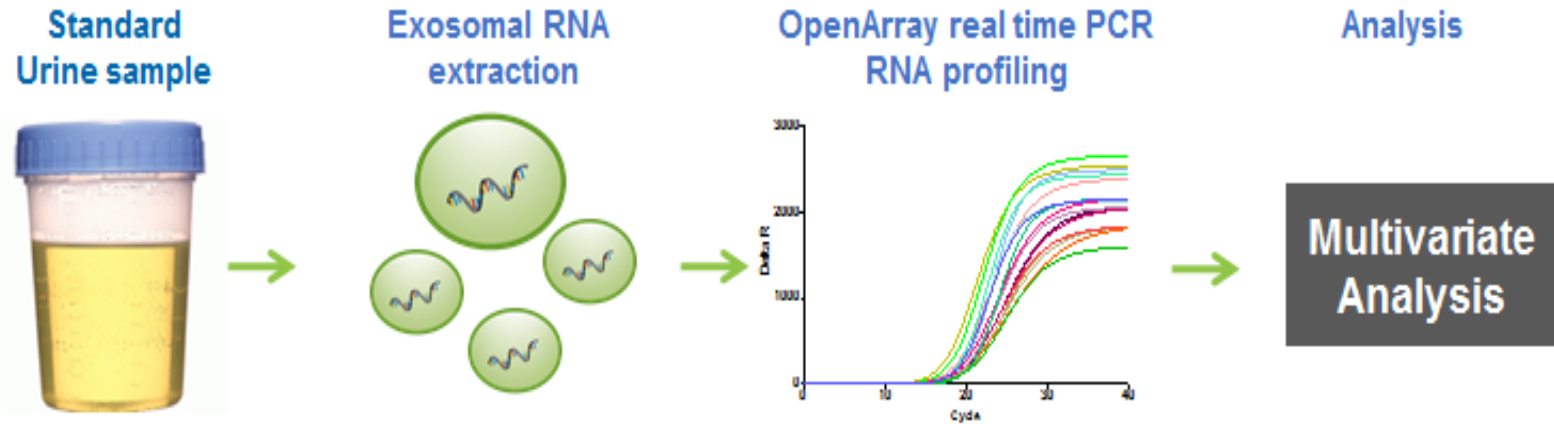
Discovery and Validation of a Urinary Exosome mRNA Signature for the Diagnosis of Human Kidney Transplant Rejection

Rania El Fekih,¹ James Hurley,² Vasisht Tadigotla,² Areej Alghamdi,¹ Anand Srivastava,¹ Christine Coticchia,² John Choi,¹ Hazim Allos,¹ Karim Yatim,¹ Juliano Alhaddad¹,¹ Siawosh Eskandari,¹ Philip Chu,¹ Albana B. Mihali¹,¹ Isadora T. Lape,¹ Mauricio P. Lima Filho,¹ Bruno T. Aoyama,¹ Anil Chandraker,¹ Kassem Safa,³ James F. Markmann,³ Leonardo V. Riella¹,¹ Richard N. Formica¹,⁴ Johan Skog,² and Jamil R. Azzi¹

Consort Flow Diagram and histologic diagnosis of enrolled patients



Sample processing workflow

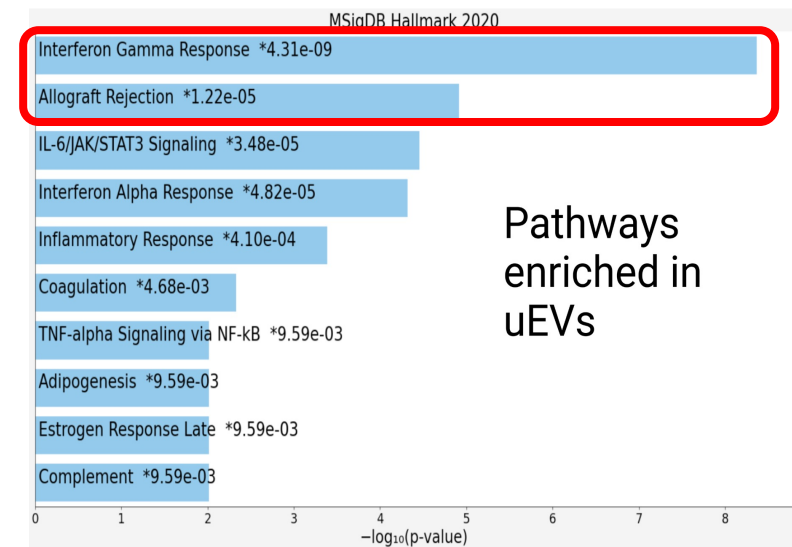
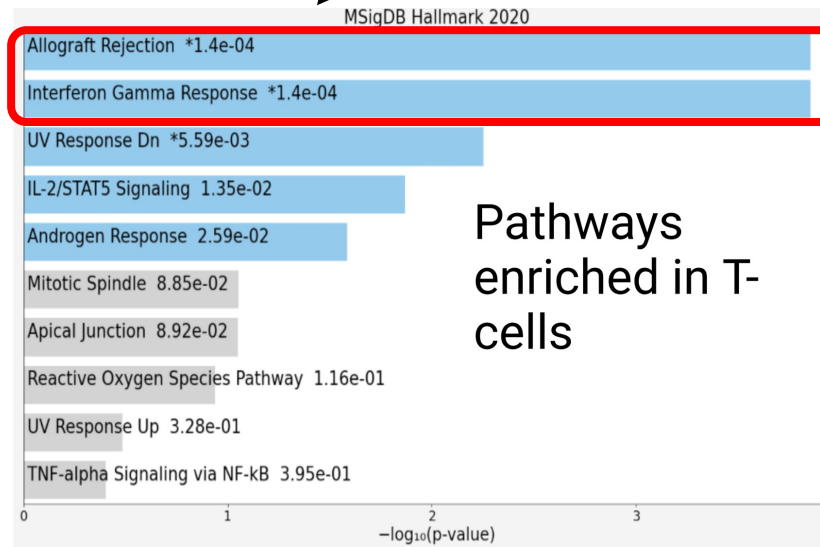
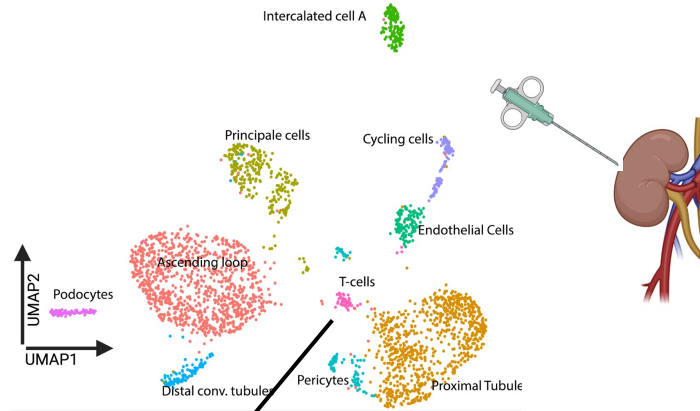


- The exosomes are isolated from the urine with EXOPRO (ExosomeDx)
- RNA reverse transcribed using the VILO cDNA synthesis kit (Thermo Fisher).
- Analyzed using the TaqMan® OpenArray® Human Inflammation

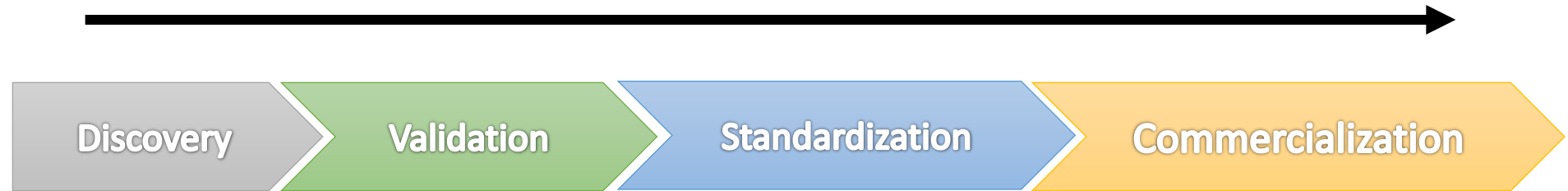
Upregulated Genes

Role in Immune activation	Gene signature	
	All cause rejection	ABMR vs TCMR
<i>Pro-inflammatory cytokines</i>	IL32 CXCL14 B2M	
<i>TGFβ superfamily</i>	BMP7	
<i>Upregulated in acute allograft rejection</i>	C3 CXCL11	C3 CXCL11
<i>Inflammasome, different inflammatory processes</i>	STAT1, TBP, NAMPT, IFNGR1, IRAK2, IL18BP, SERPINA1	IFNAR2
<i>Regulating protein trafficking, dendritic cell migration and T lymphocytes homing</i>	CD74	CD74 CD44





Phases of Biomarkers Discovery

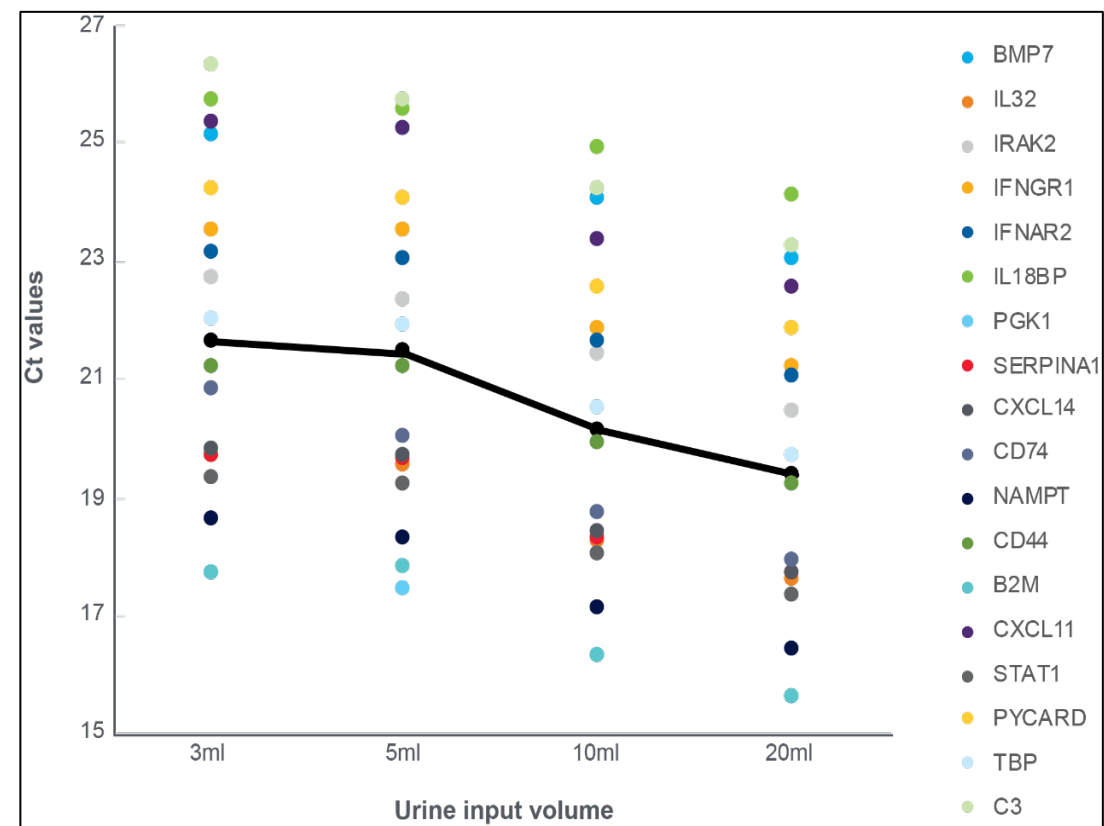


- Targeted or non-targeted approaches
- High-throughput technologies
- Identify a panel

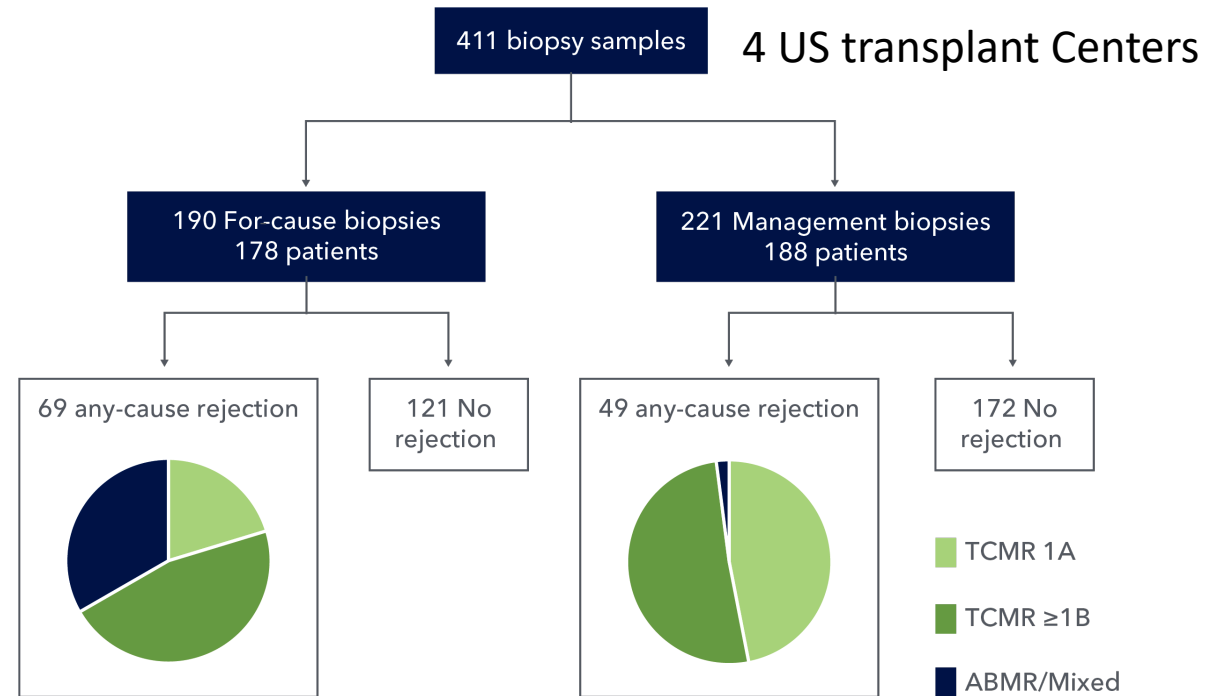
- Use independent samples
- Identify a refined set
- Prospective multicentral validation

- Laboratory equipment
- Reagents
- Can the test be reproduced in different laboratories

Transfer the signature to a clinical platform

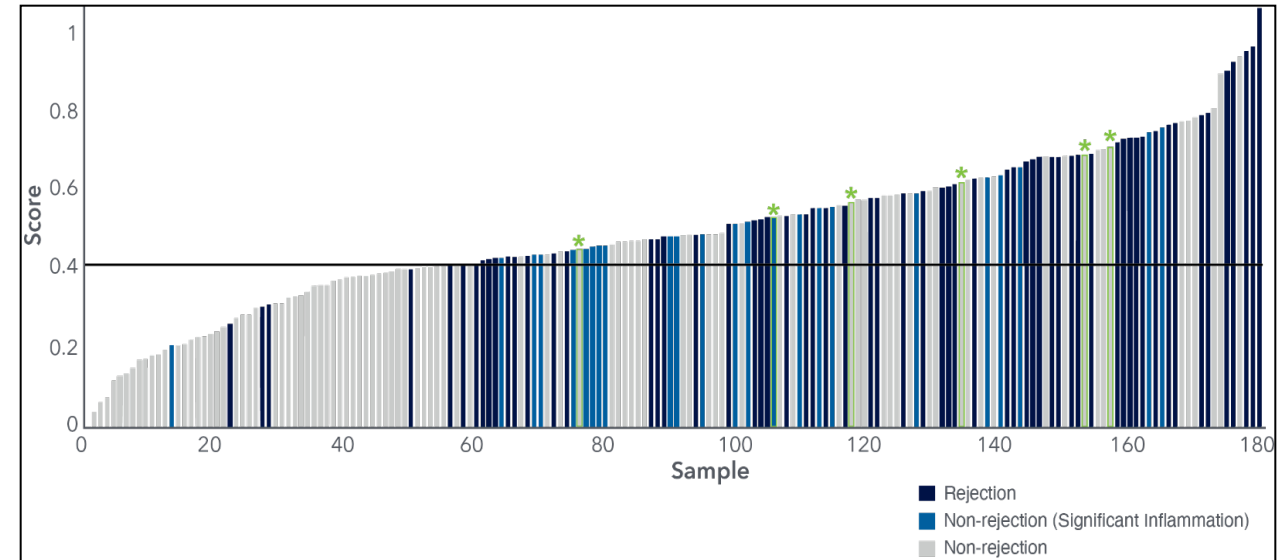
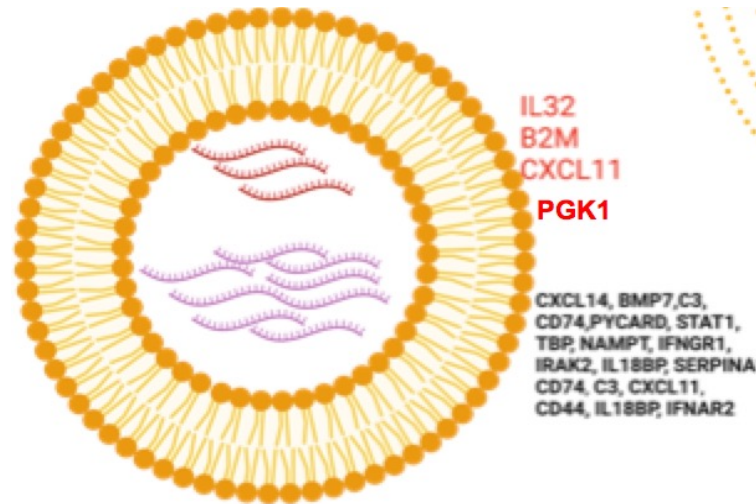


Validation study reflecting real-life



Biopsies with inflammation, such BKV associated nephropathy, Interstitial Nephritis, Recurrent Glomerulonephritis or IC deposition—were not excluded from analysis.

Role of Inflammation in Classification: Results for Clinically Indicated Biopsies



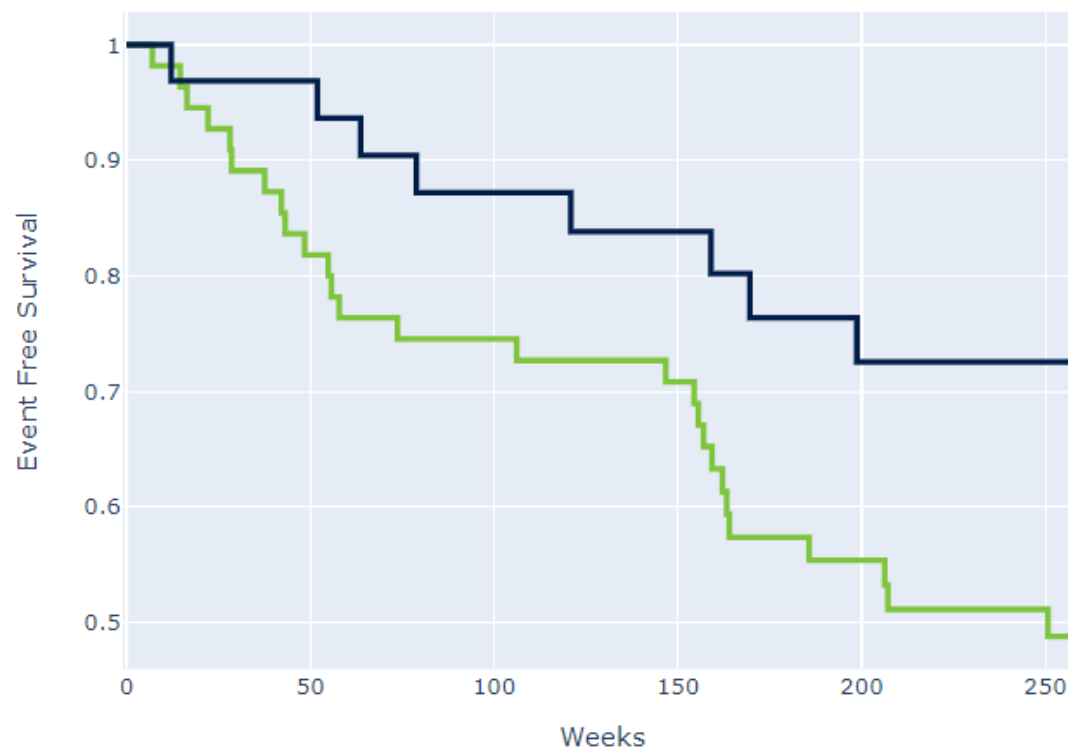
	<u>Any-cause rejection only</u>		<u>Any-cause rejection or significant inflammation</u>	
<u>Metrics</u>	<u>Point estimate</u>	<u>Confidence interval</u>	<u>Point estimate</u>	<u>Confidence interval</u>
Sensitivity	0.93	(0.841-0.982)	0.94	(0.868-0.981)
<u>Specificity</u>	0.43	(0.34-0.523)	0.53	(0.422-0.628)
PPV	0.45	(0.364-0.543)	0.63	(0.544-0.719)
NPV	0.93	(0.827-0.98)	0.91	(0.804-0.97)
<u>Unnecessary biopsies avoided</u>	43%	(34%-52%)	53%	(42%-63%)

Significant inflammation

- pathologic lymphoproliferative infiltrate
- moderate to severe lymphocytic infiltration
- interstitial nephritis (BKV nephritis or acute interstitial nephritis)
- glomerulopathy, or immune complex deposition)

Prognostic Potential: ExoTRU score is associated with 5 years outcome

HR=2.23, p-val=0.023

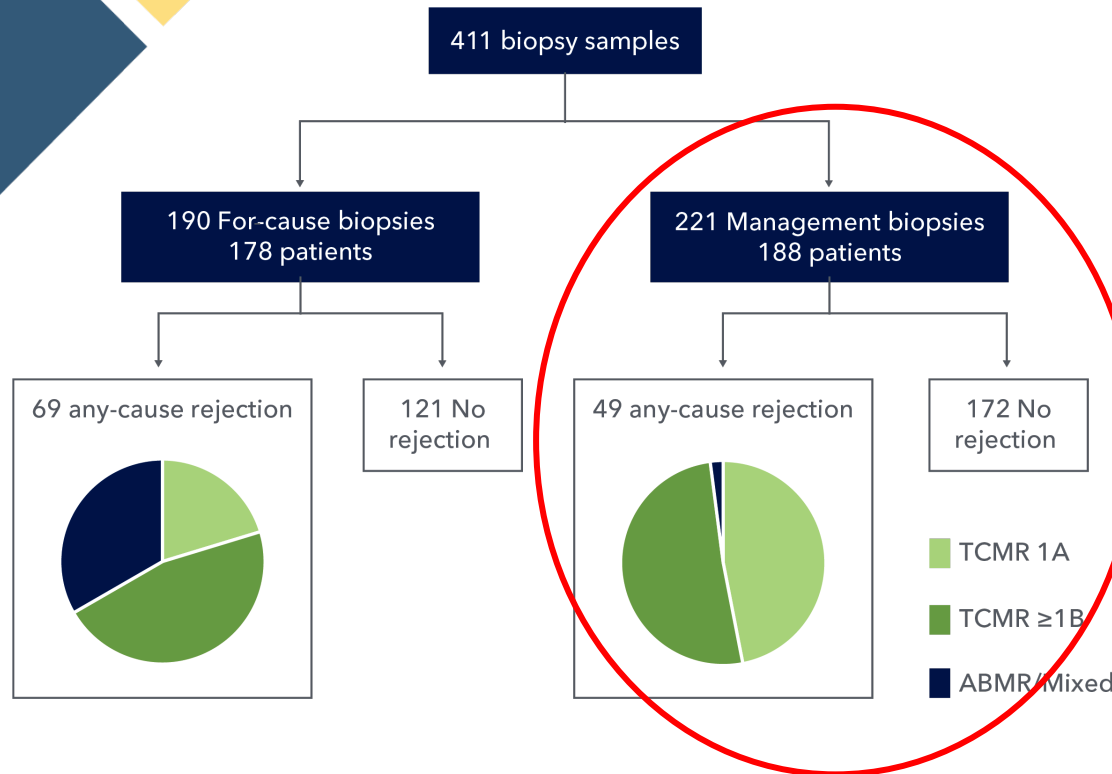


Five-Year Composite Endpoints:

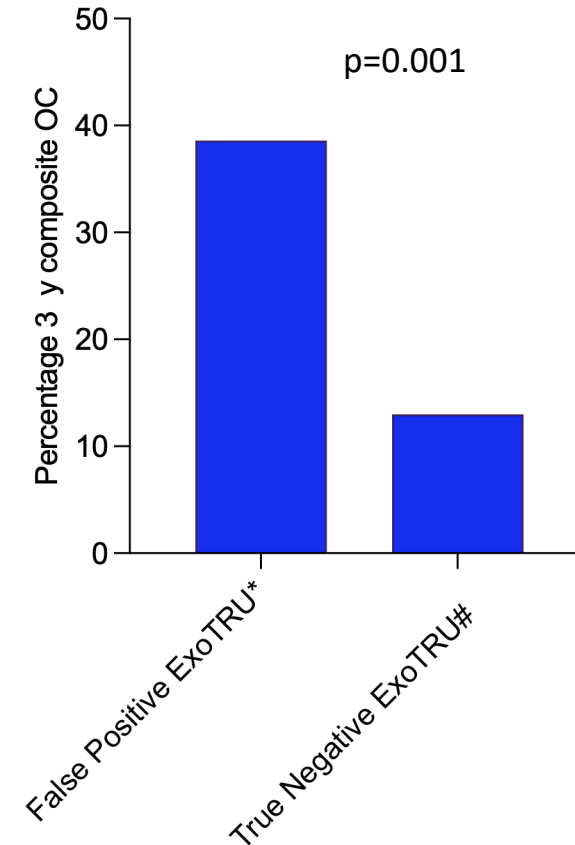
- >30% decrease in eGFR
- Subsequent rejection
- De novo DSA
- Loss of graft with either return to dialysis or re-transplant

Prognostic Potential: ExoTRU score is associated with 3 years outcome

ExoTRU at 3 months Post Transplant



IFNAR2, PYCARD, CD44, IRAK2, B2M and NAMPT
PGK1



Unpublished data



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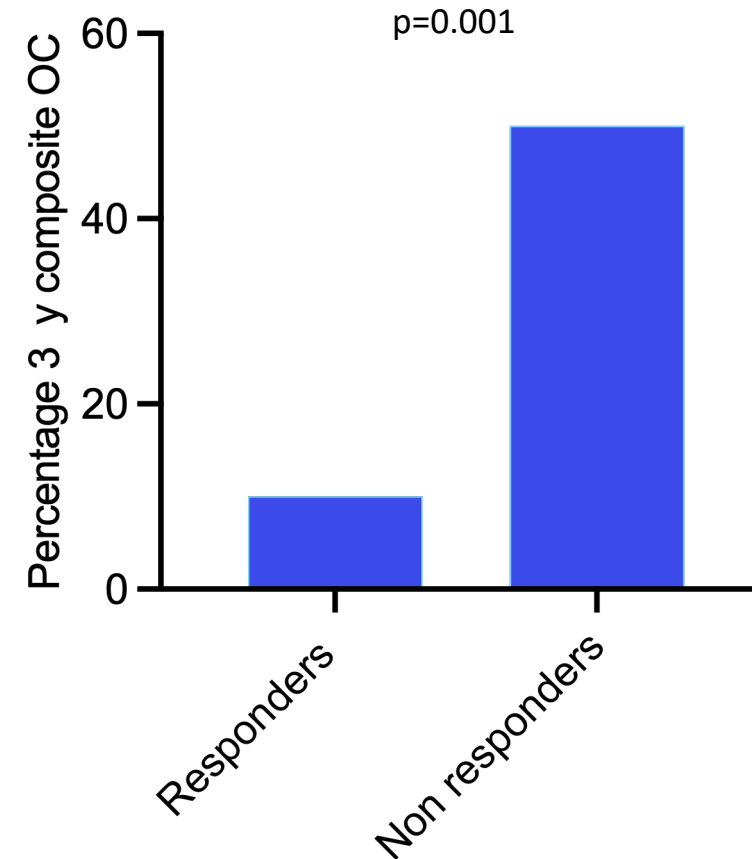
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Predictive Potential: ExoTRU scores correlate with response to treatment and 3 years outcome

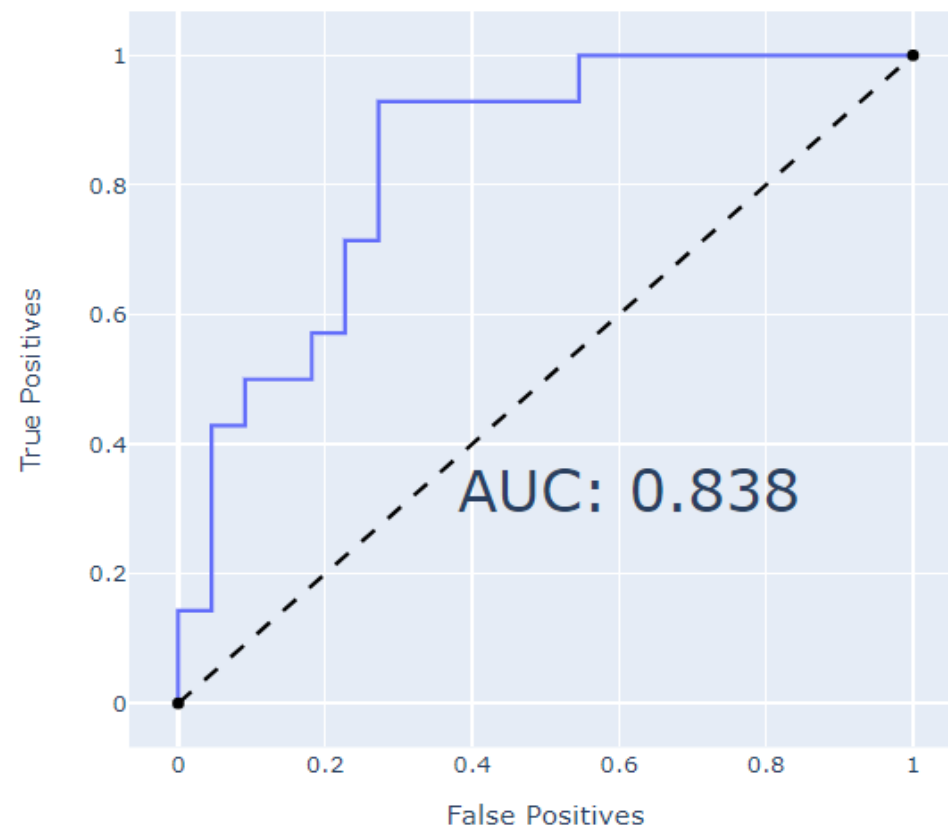
23 samples from patients who have had a repeat ExoTRU score after being treated for rejection, we looked at the change in score after treatment.

Responders: patients who showed at least 30% decrease in the urinary score after treatment.

Non responders: score increased or was stable after treatment



Independent Validation By Thermo Fisher



ExoTRU



EKTRA



One Lambda Pre-Transplant Risk Assessment Assay

A test leveraging a unique RNA signature pre-transplant that provides information about post-transplant graft function and immunosuppression status in deceased-donor kidney transplant recipients.

[Learn more](#)

MMDx for Molecular Gene Expression Biopsy Assessment

Innovative software leveraging gene expression data from biopsied heart and kidney tissue. This service can provide information that can supplement diagnoses of allograft injury via histopathology and other parameters.

[Learn more](#)

TacroType™ Pharmacogenetic Test

TacroType is a pharmacogenetic test designed to assess genetic variation in the CYP3A5 gene that affects how a transplant patient metabolizes tacrolimus. The test helps provide insights that transplant teams may use to inform dosing decisions from the very first dose.

[Learn more](#)

One Lambda Devyser Chimerism NGS Assay

Designed to provide accurate and sensitive detection of microchimerism levels in stem cell transplant samples, the One Lambda Devyser Chimerism NGS assay is an ideal choice for HLA and molecular core labs associated with HSCT Programs.

[Learn more](#)

One Lambda Devyser Accept cfDNA Assay

An NGS-based assay developed for clinicians and HLA laboratories to detect cell-free DNA in human plasma samples. This assay provides high sensitivity, with minimal hands-on time and results in as little as 24 hours.

[Learn more](#)

One Lambda CXCL10 Assay

Noninvasive urine-based test that can detect the CXCL10 chemokine in human urine samples for kidney transplantation. Multiple studies have shown that elevated CXCL10 is associated with inflammation and early graft dysfunction.

[Learn more](#)

Antibody monitoring assays

HLA donor specific antibodies (DSAs) are linked to transplant rejection. Our reliable, high-sensitivity single-bead assays offer optimal antibody monitoring for better transplant care.

[Learn more](#)

One Lambda Exosomes Kidney Transplant Assay

EkTRA is a rapid, non-invasive urinary assay utilizing qPCR technology to evaluate exosomal mRNA.

[Learn more](#)

More than meets the eye

19 yo male with history of ESRD secondary to congenital kidney disease S/P deceased kidney transplant 1/24/26 (KDPI 46%), 4 HLA MM, PRA 0% induced with thymo.

Had multiple GI symptoms and had Mycophenolic Acid switched to Imuran and dose reduced due to leukopenia and EBV viremia detected in a high risk patient.

Creatinine plateaued around 2.

Biopsy done 4/6: No rejection

Creatinine worsened

Biopsy done 4/28: ACR and AMR.

EKTRA 3/30/26: 0.7 in favor of rejection

Lessons learned at BWH: EKTRA in the Clinic

- Excellent rule out test
- Stable kidney function and no proteinuria with EKTRA positive-> Many cases of ABMR and ACR from borderline to 2A
- cfDNA negative but EKTRA positive: Few cases showing biopsy with active disease from interstitial inflammation to ACR IB and partially treated ABMR.
- Patients with history of ESRD secondary to IgA nephropathy with positive EKTRA post transplant-> IgA nephropathy recurrence even in the absence of proteinuria and hematuria.
- EKTRA positive but biopsy normal: High Risk patients.
- Limitations: Preemptive Transplantation, urine infections...

Building a Complete Translational Pipeline

Connecting human Findings to advanced therapeutic development



Bridging the Gap

Connecting human sample findings to small animal models and non-human primates.



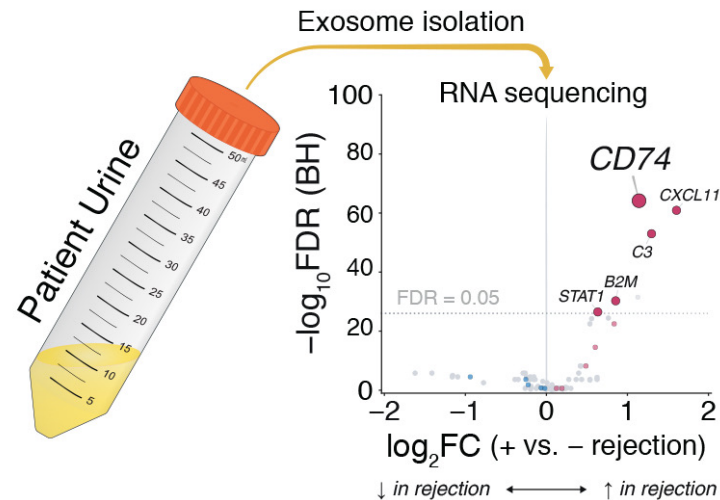
Therapeutic Platforms

Developing in-house or partnered platforms for biologics, gene therapies, and small molecules.

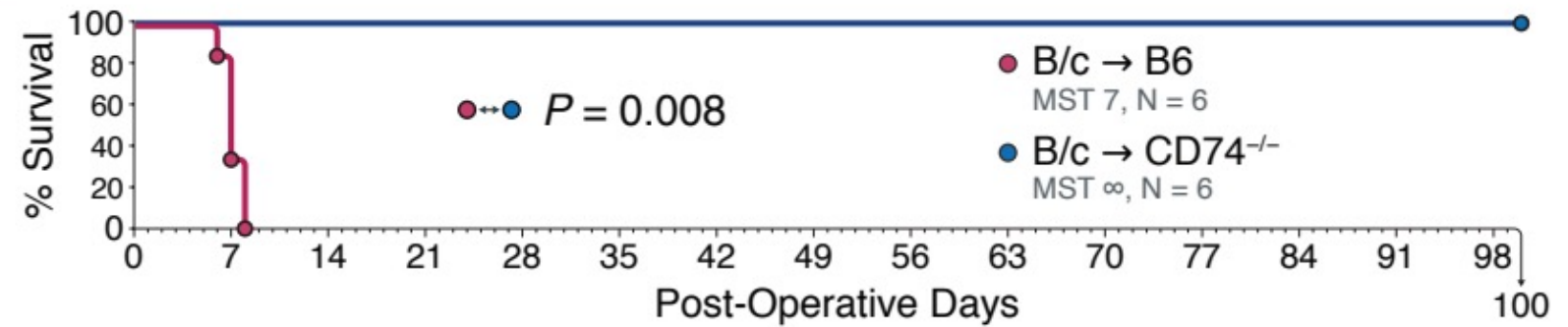
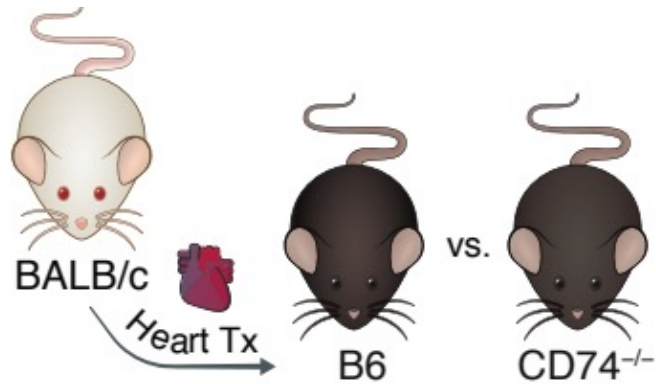


AI-Powered Discovery

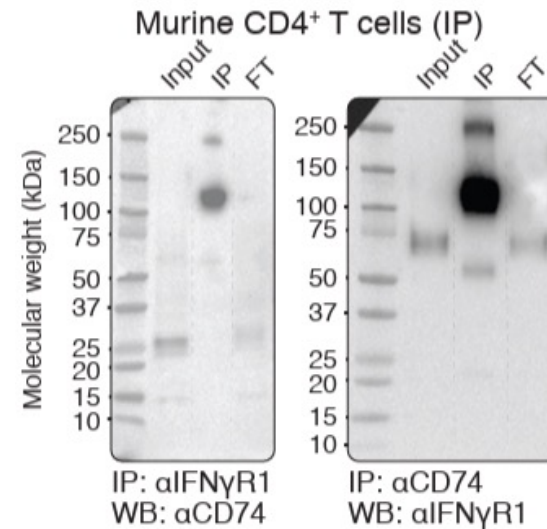
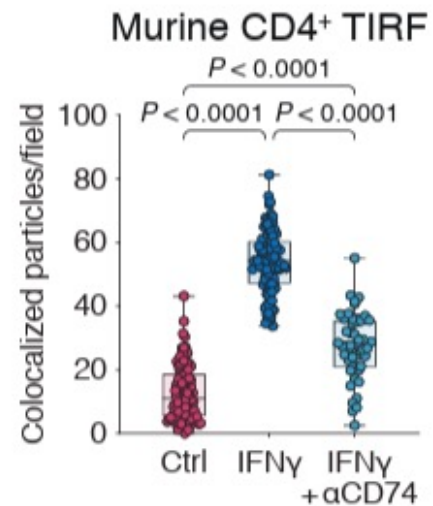
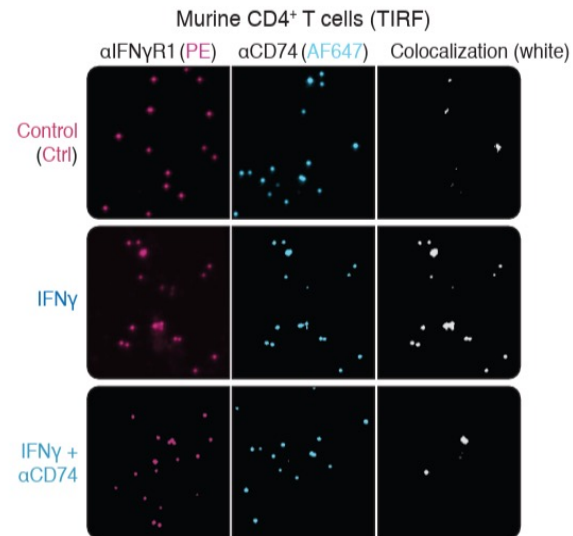
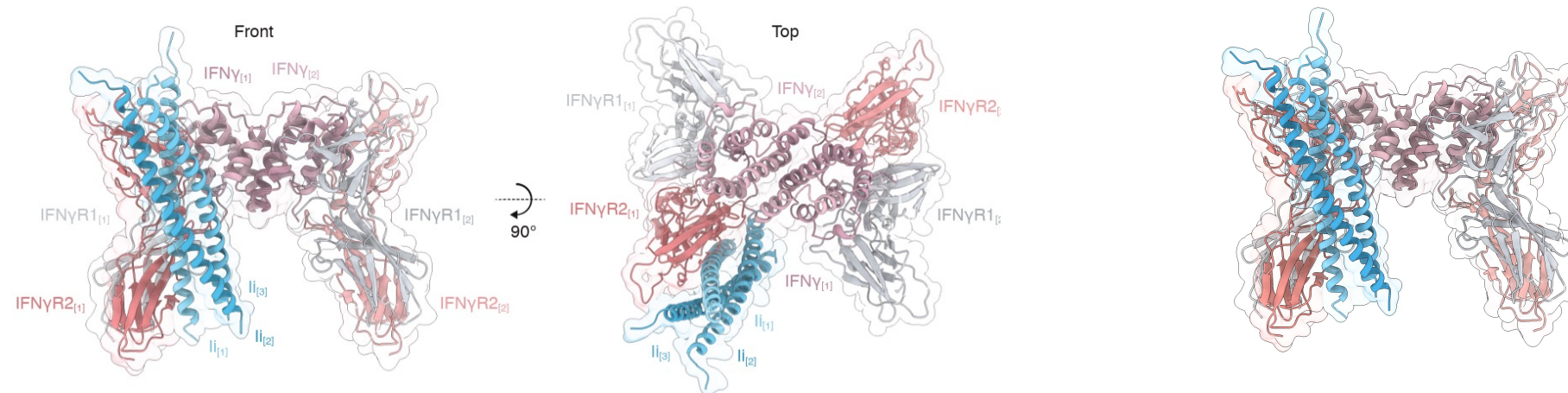
Harnessing AI for virtual drug screening and drug repurposing.



From humans back to mice

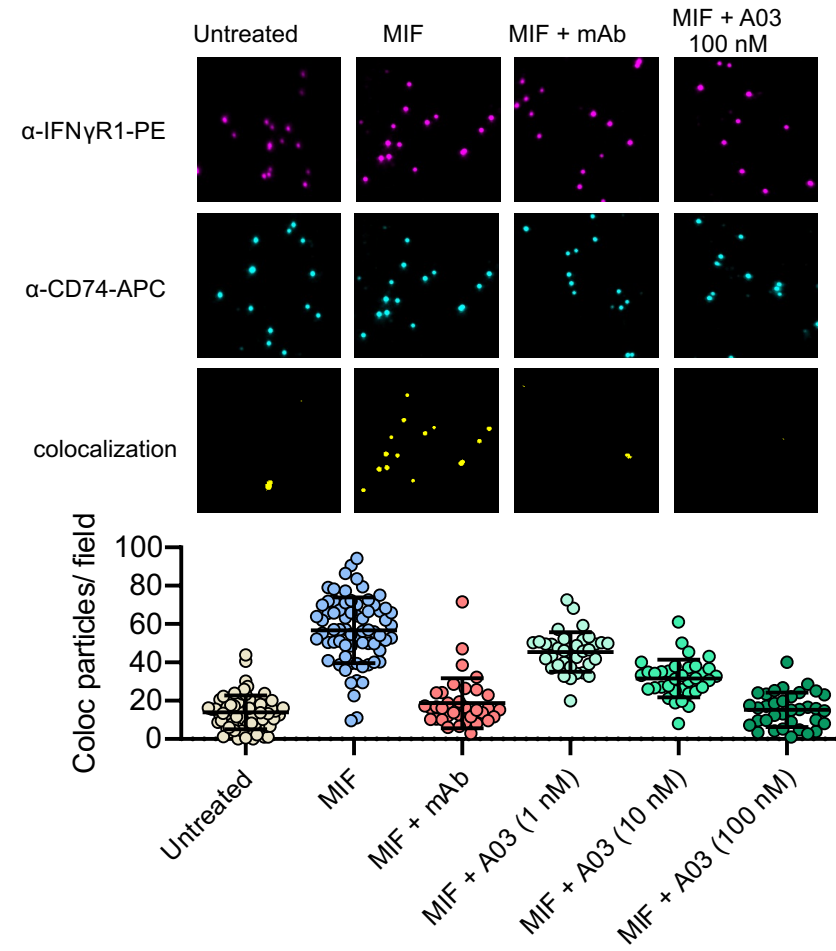


CD74 colocalize with the interferon-gamma receptor (IFN γ R) and facilitate IFN γ signalling.



Unpublished data

Compound interaction with CD74



THE FUTURE: URINE MOLECULAR SIGNATURES

GUIDING PERSONALIZED THERAPY FOR KIDNEY TRANSPLANT RECIPIENTS

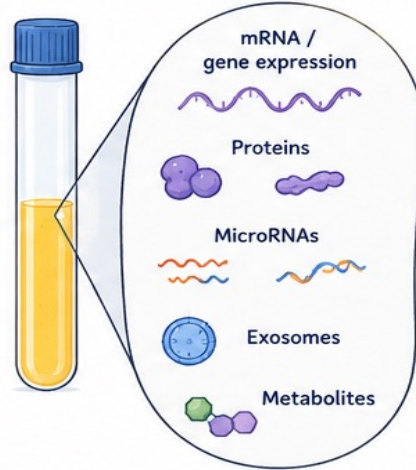
A simple urine test. Deep molecular insight. Personalized care.

1. A SIMPLE SAMPLE



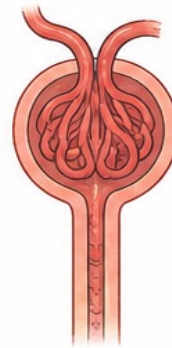
2. MOLECULAR SIGNATURES

What's in the urine?



3. PATHWAY INSIGHTS

What's happening in the allograft?



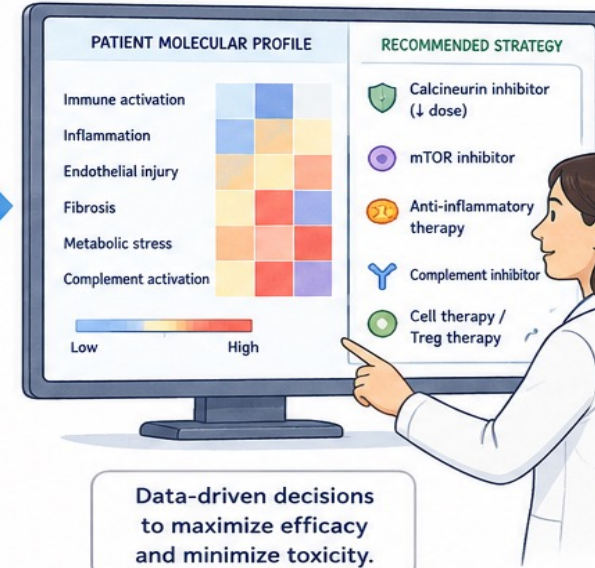
Key Pathways

- Immune activation
- Inflammation
- Endothelial injury
- Fibrosis
- Metabolic stress
- Complement activation

Molecular signatures reveal active pathways before clinical signs.

4. PERSONALIZED THERAPY

Right drug. Right dose. Right patient.



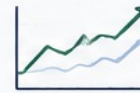
THE VISION



Detect problems early
Intervene early



Personalize therapy
for each patient



Improve graft survival
and patient outcomes



Reduce toxicity
Improve quality of life

From a urine sample to precision care — transforming outcomes for every transplant recipient.



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TRANSPLANTATION RESEARCH CENTER

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- Rania El Fekih
- David Cuchiari
- Siawosh Eskandari
- Xi Xia
- Nour Younis
- Nadim Rahy
- Hengcheng Zhang
- Dongliang Zhang
- Zhabiz Solhjoui
- Houda Djebly
- Tao, Lao
- Soltan Alchaar
- Anis Joseph Saad
- Jean Pierre Assaker
- Farnaz, Namazi
- Areej Alghamdi
- Andrew Badaoui
- Ina Sulkaj,
- Mostapha Tawfeeq
- Kate Cashman
- Ahmad Halawi

Collaborators:

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James Hurley PhD
Vasist Tadigotla PhD
Bryan Haynes PhD
- Thermo Fisher:
Bethany Dale
Marc Rumpler
Alexandre Vlassov
- MGH:
Hakho Lee PhD
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Leo Riella MD, PhD
Kassem Safa MD
- Yale:
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- University of Pittsburgh:
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Camila Macedo PhD
- AUB:
Pierre Khouery PhD
Abdullah Kurdi
- Broad Institute:
Anna Greka MD, PhD

TRC:

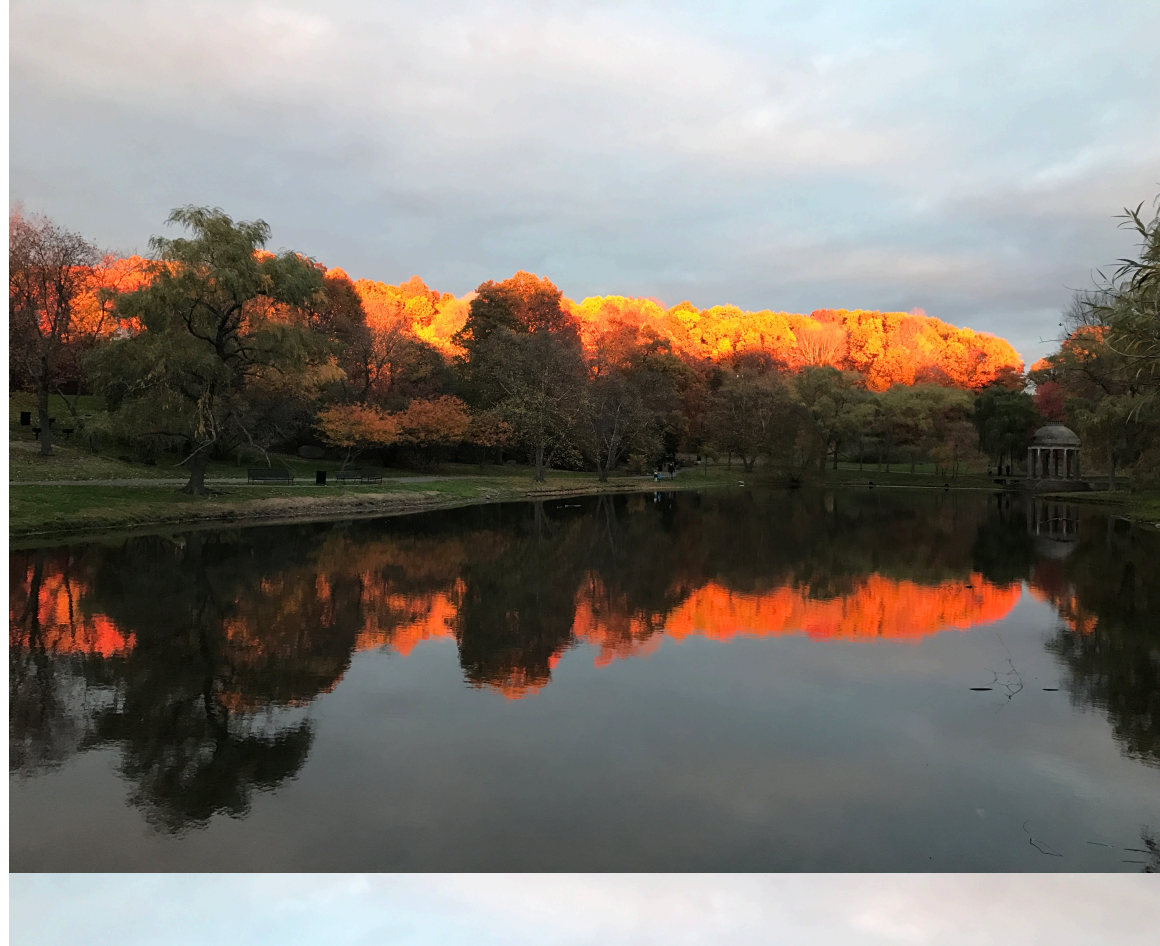
- Reza Abdi
- Martina McGrath
- Melissa Yeung
- Peter Sage
- Naoka Murkami
- Mohammed Sayegh

Funding sources:





Questions and different perspective?



Autumn,
the season that teaches us that change can be beautiful



@azzilab
@jazzitup



Thank you

jazzi@bwh.harvard.edu

*Visit the Azzi lab at
Jazzilab.bwh.harvard.edu*

Thank you

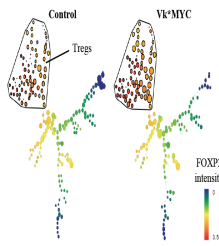
jazzi@bwh.harvard.edu



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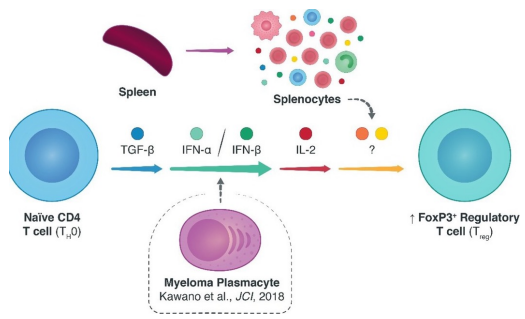
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Tregs homeostasis

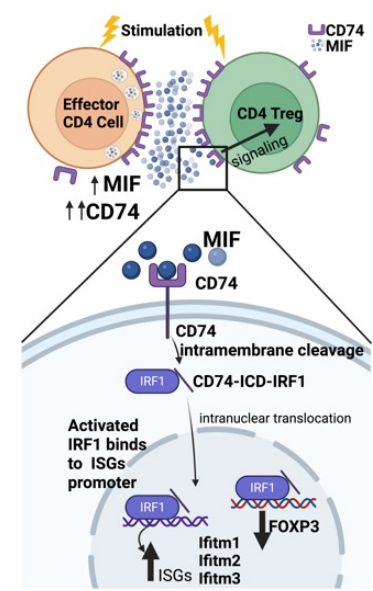
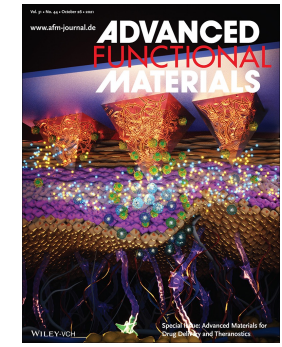
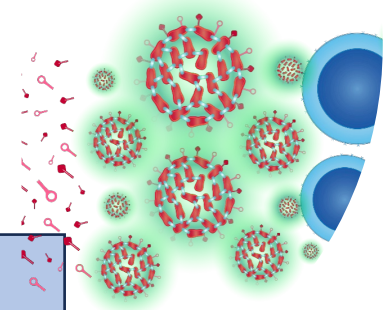
Type 1 Interferon

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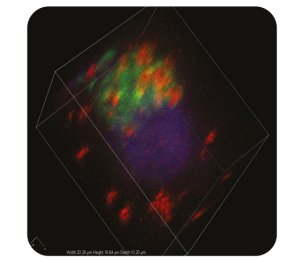
IL2 signaling

- 1- Eskandari et al. (Science TM, 2020)
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Granzyme mediated suppression

- 1- Karreci et al. (JCI, 2017)
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- 3- Eskandari et al. (Frontiers, 2022)



Unpublished data

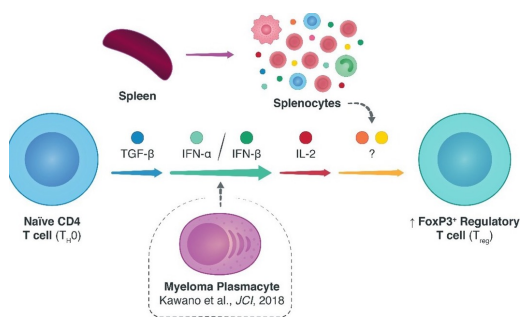
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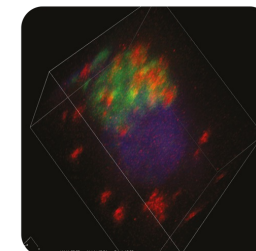
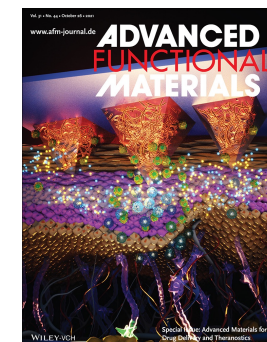
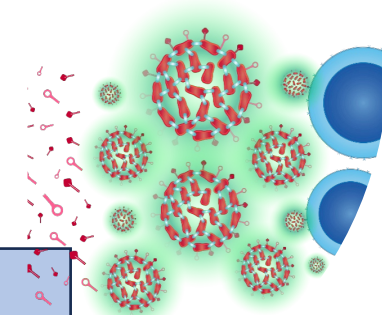


CD74 signaling

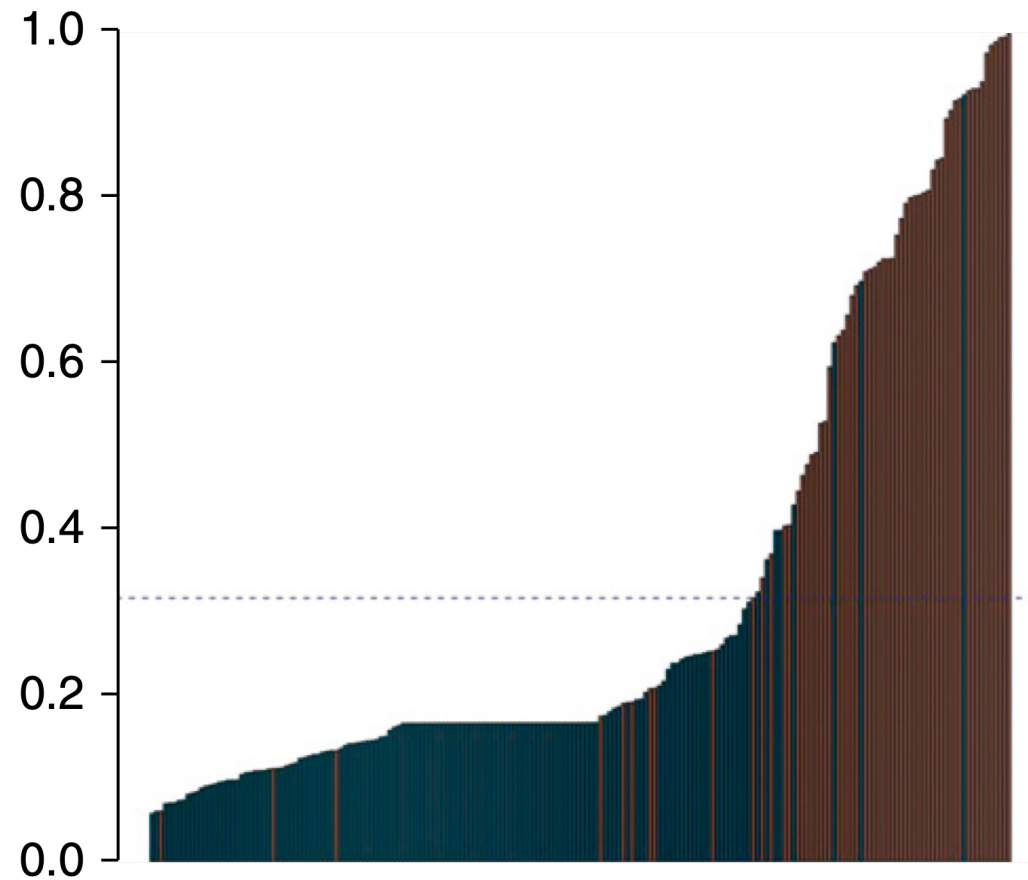
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Unpublished data



Waterfall plot of the urine exosome gene scores.

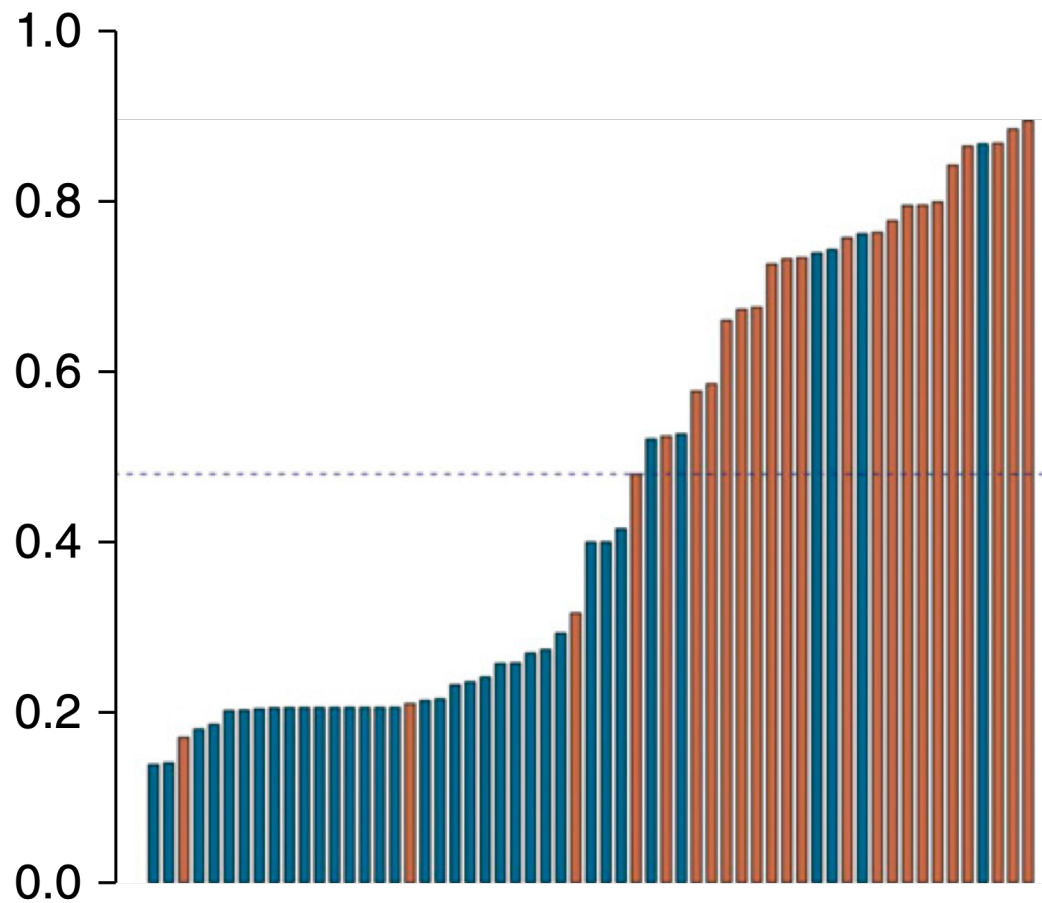


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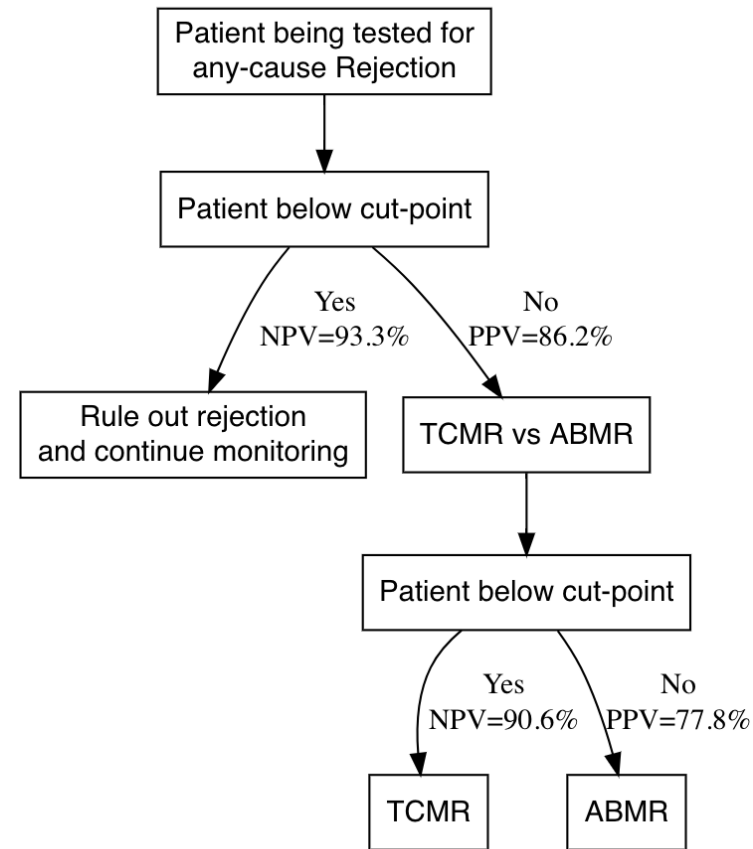


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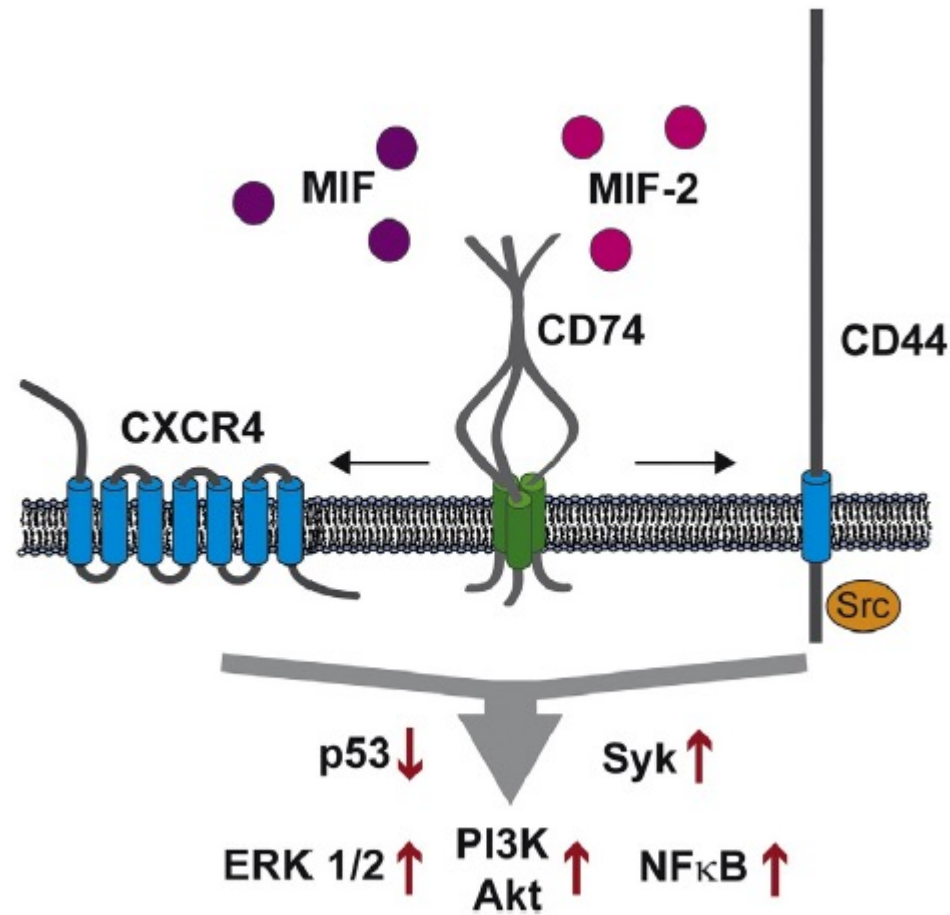
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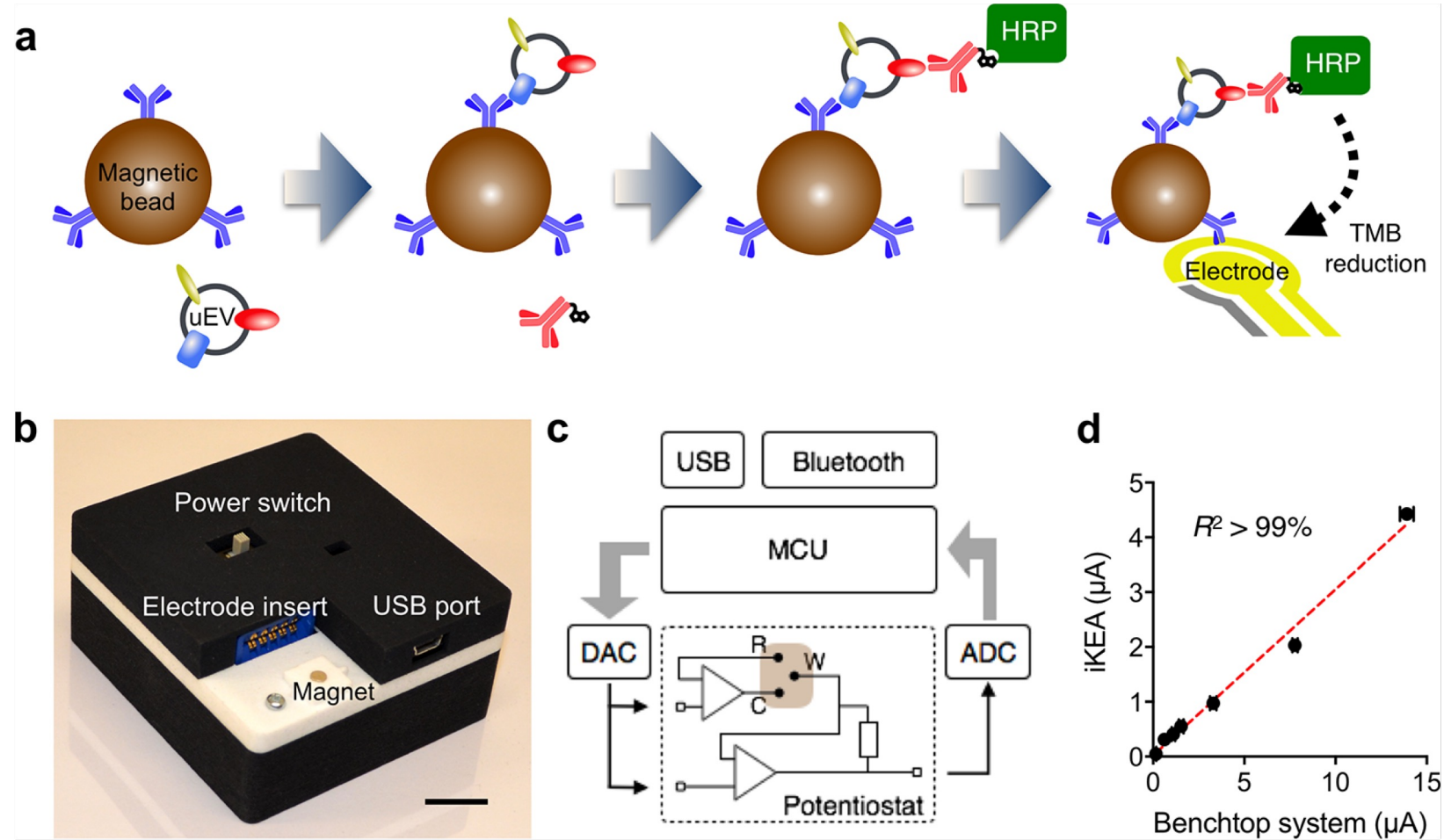
Evaluation chart for kidney transplant recipients



CD74 as a Macrophage Migration Inhibitory Factor (MIF) Receptor



Integrated Kidney Exosome Analysis (iKEA)

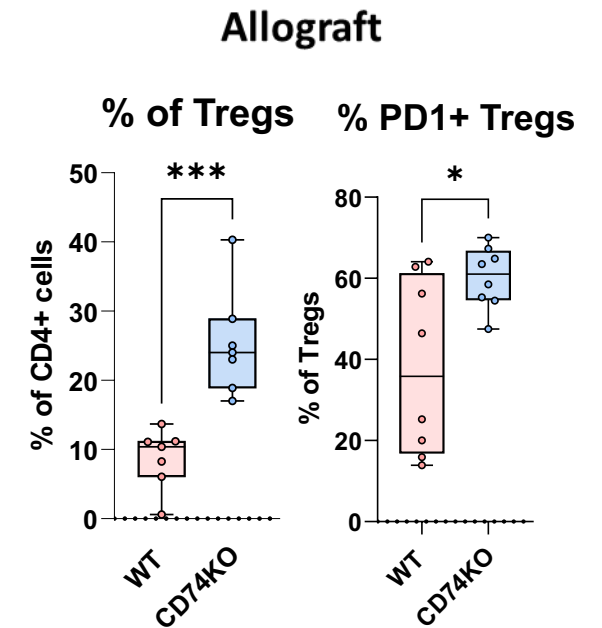
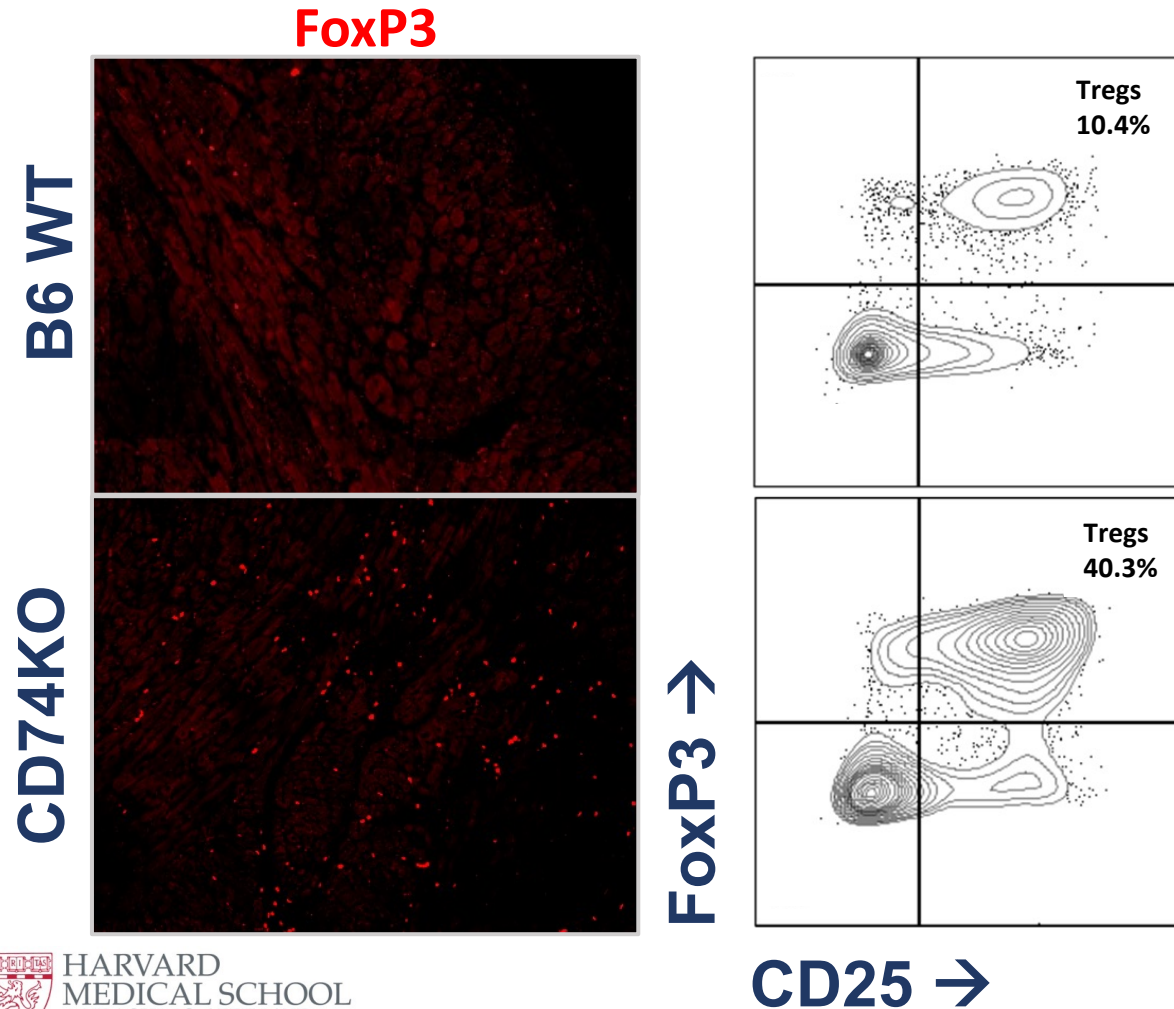


Ideal Biomarker

- Sample entire graft (avoid bias from sampling error)
- High positive and negative predictive value
- Diagnose rejection (acute and/or chronic) before its occurrence
- Uncover over-immunosuppressed/identify tolerant states
- Rapid
- Responsive
- Non-invasive
- Inexpensive

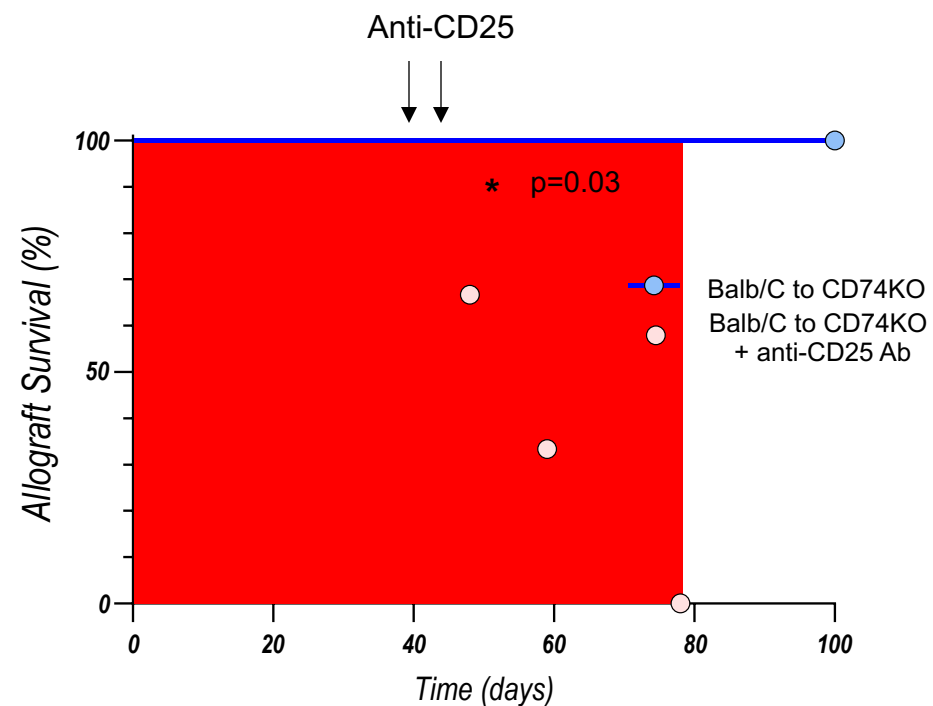


CD74KO Recipient's Allograft Show Heightened Treg Infiltration

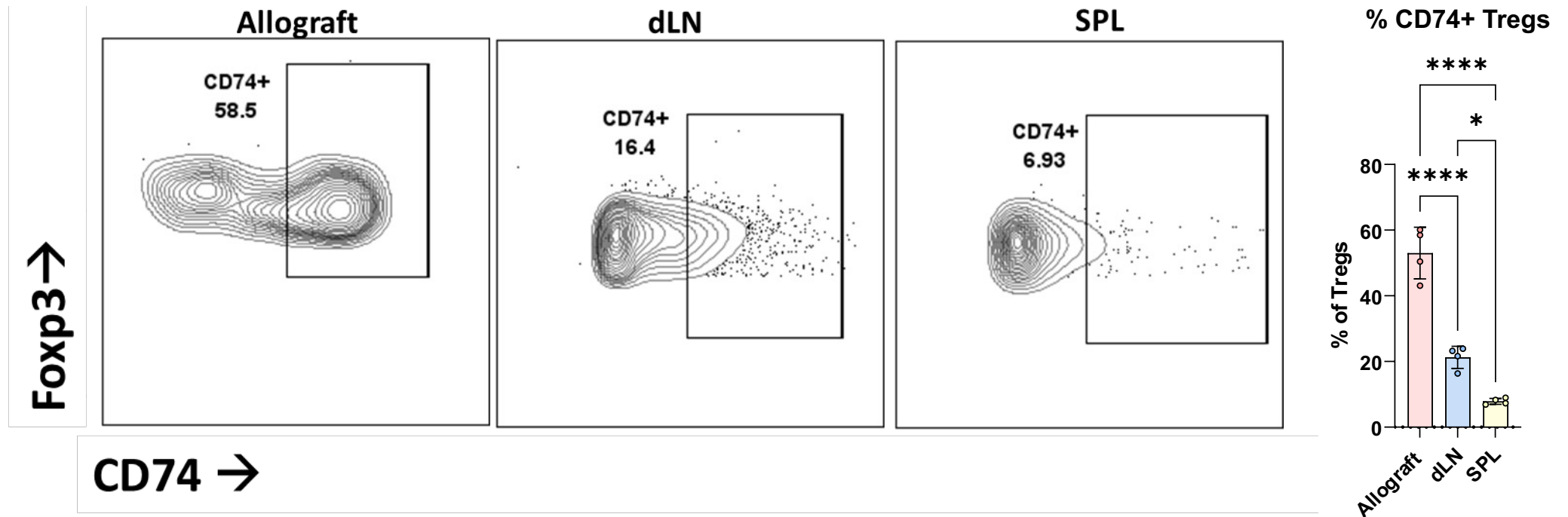


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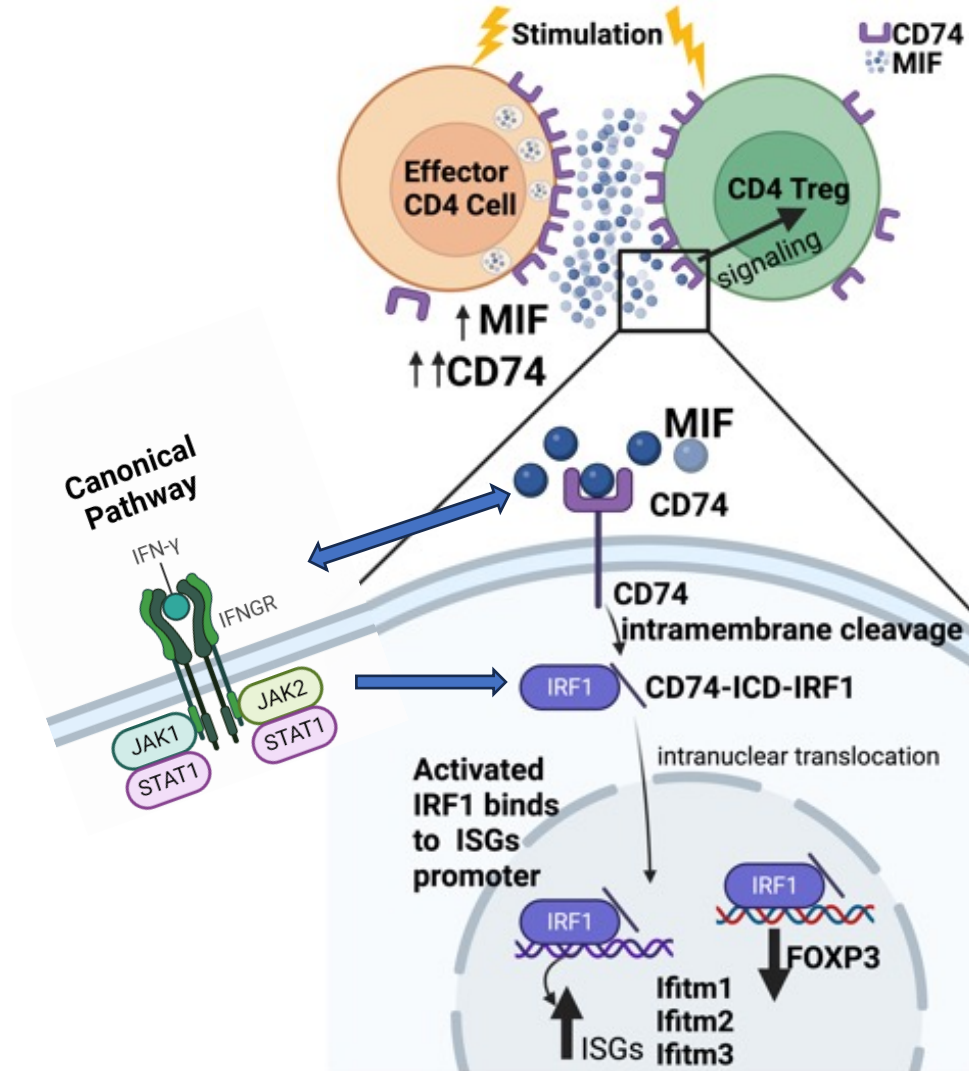
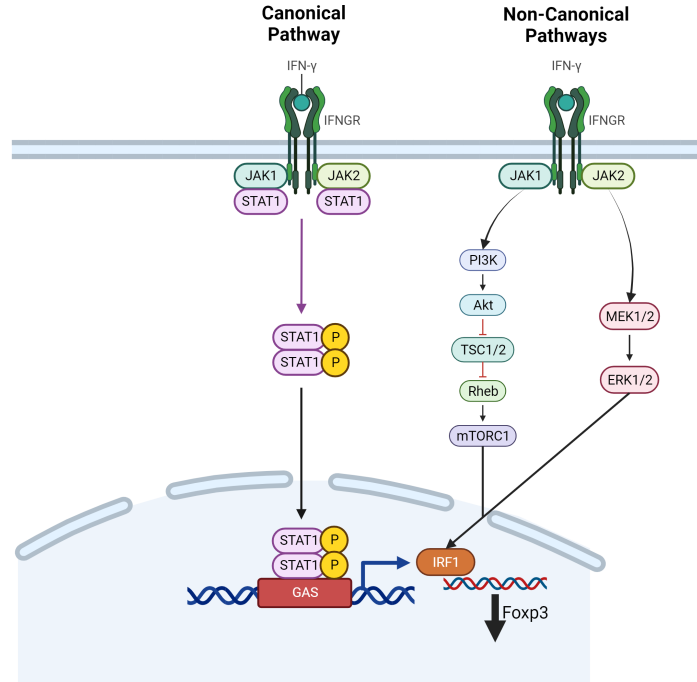
Tregs Depletion Results in Allograft Rejection

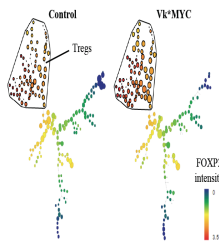


Frequency of CD74+ Tregs Increases in Allograft and Draining Lymph Node



MIF-CD74 pathway inhibits Tregs homeostasis, function and stability with potential collaboration from IFN γ

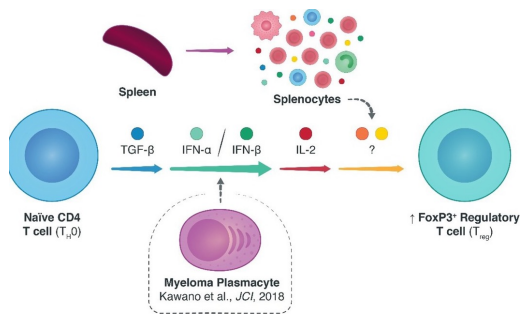




Tregs homeostasis

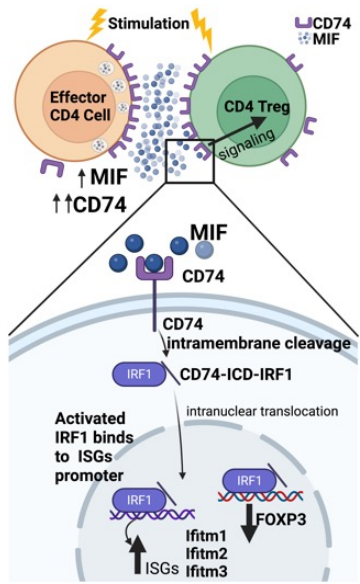
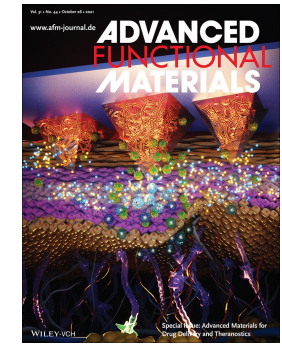
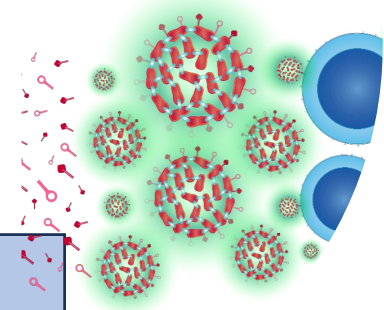
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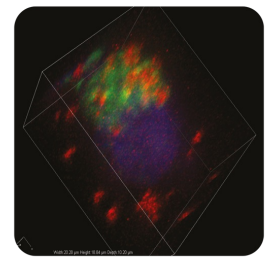
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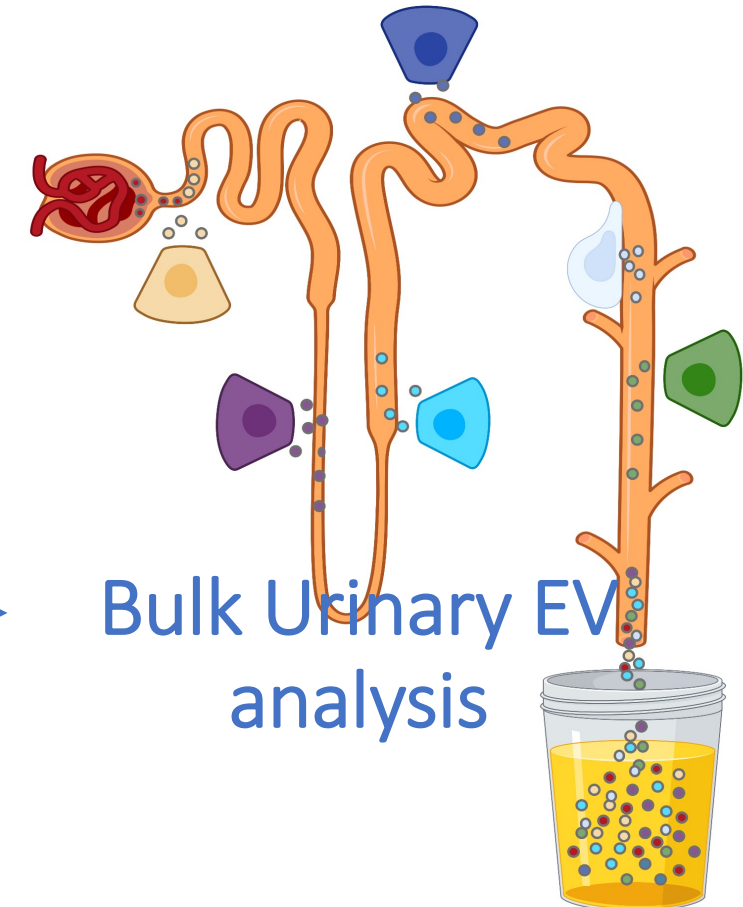
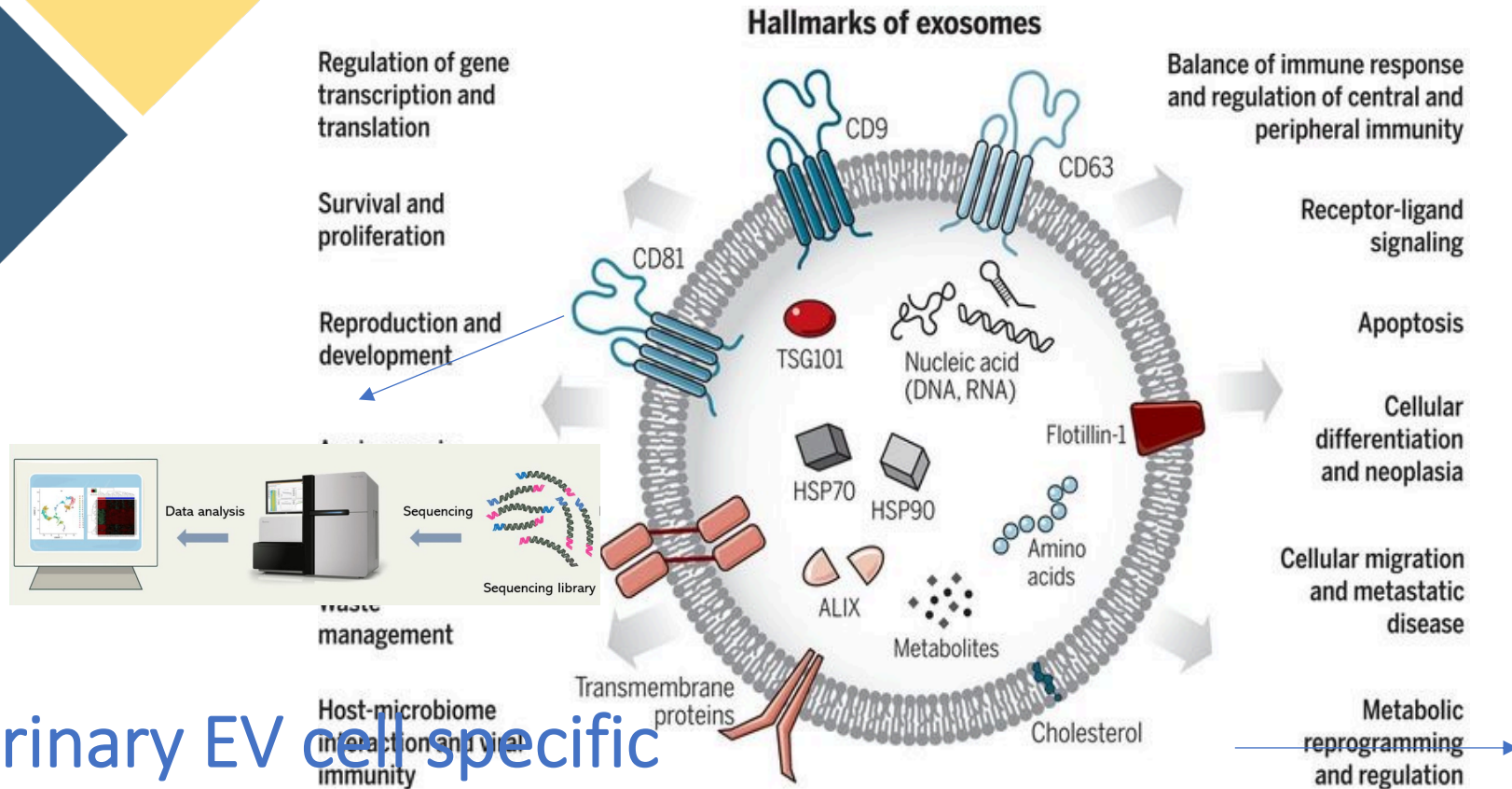


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High Throughput approach of discovery



Urinary EV cell specific signatures

The biology, function, and biomedical applications of exosomes, Volume: 367, Issue: 6478, DOI: (10.1126/science.aau6977)



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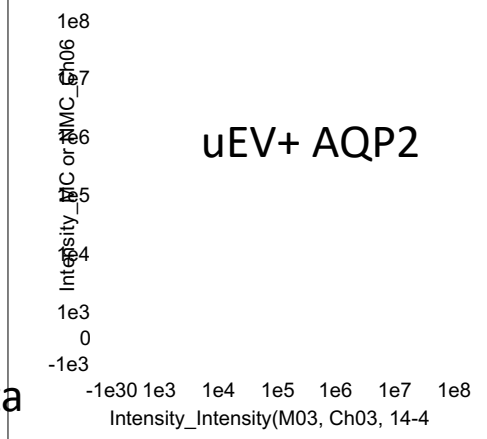
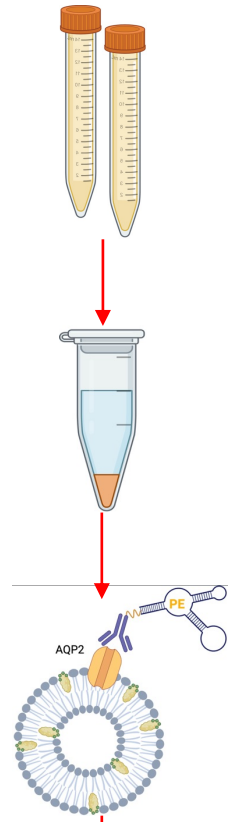
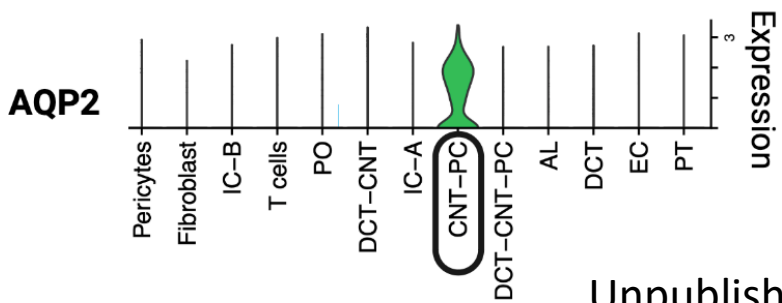
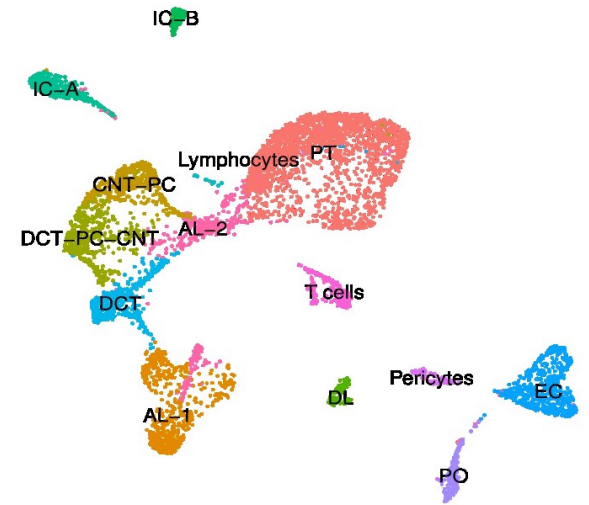
Cell specific EV signature



Surface Protein Specific for
Kidney Cells

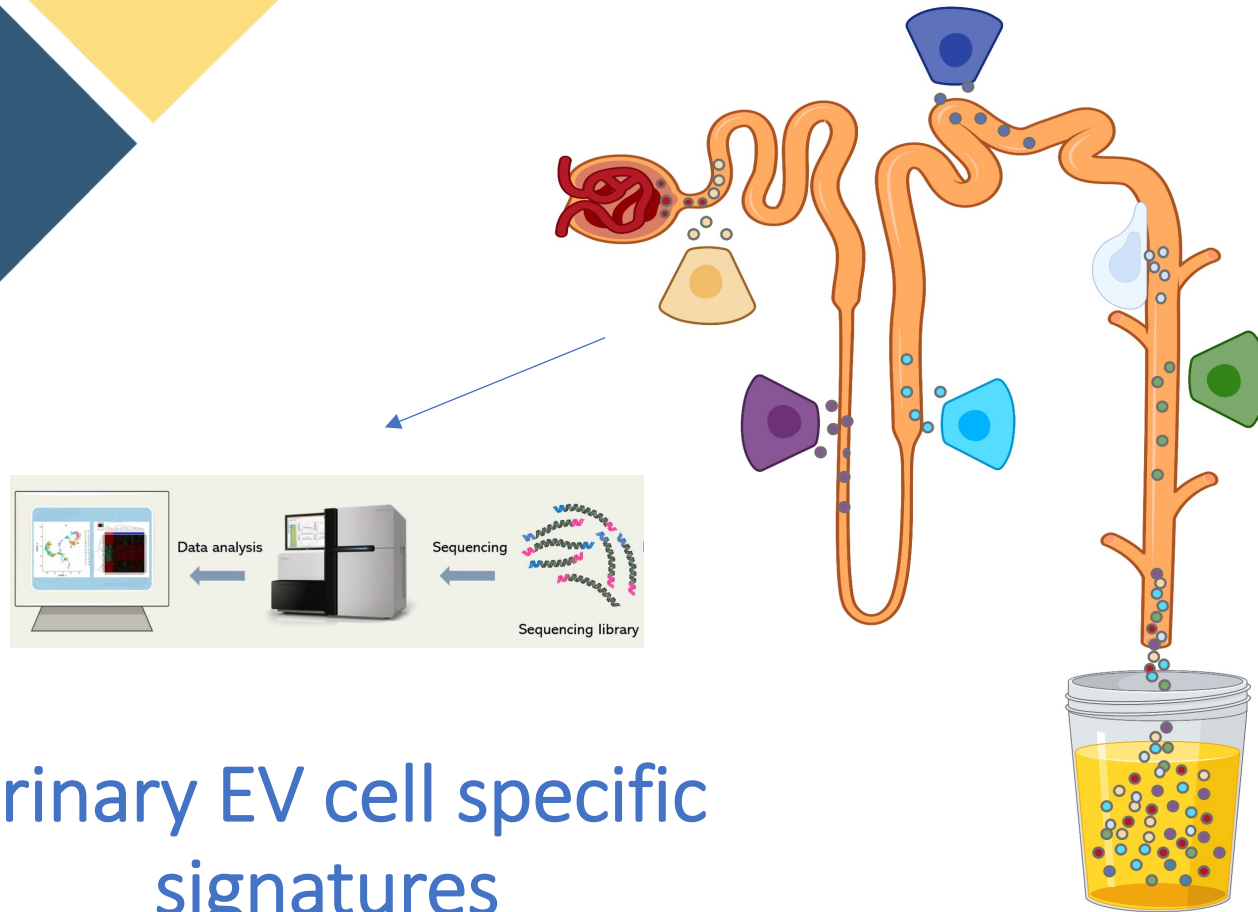
+

Present on EVs



Unpublished data

High Throughput approach of discovery



Urinary EV cell specific
signatures

Bulk Urinary EV
analysis

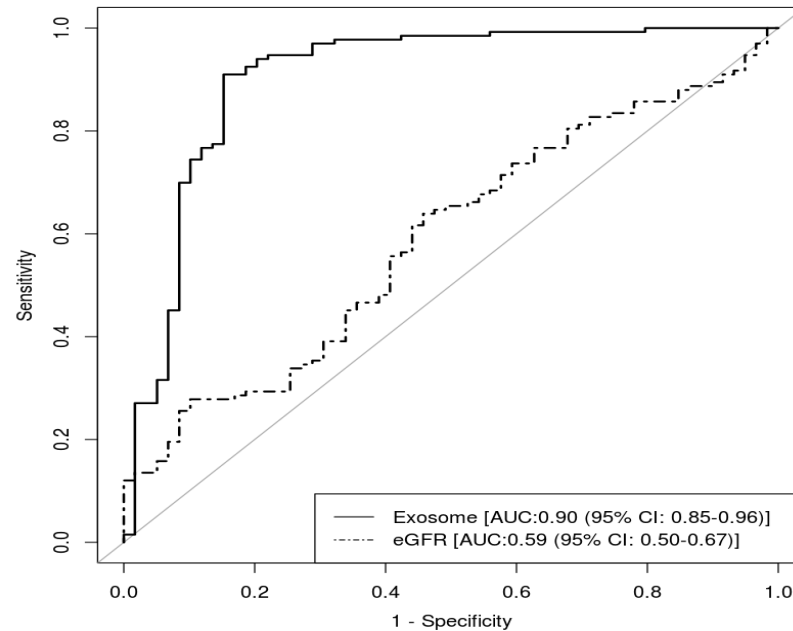


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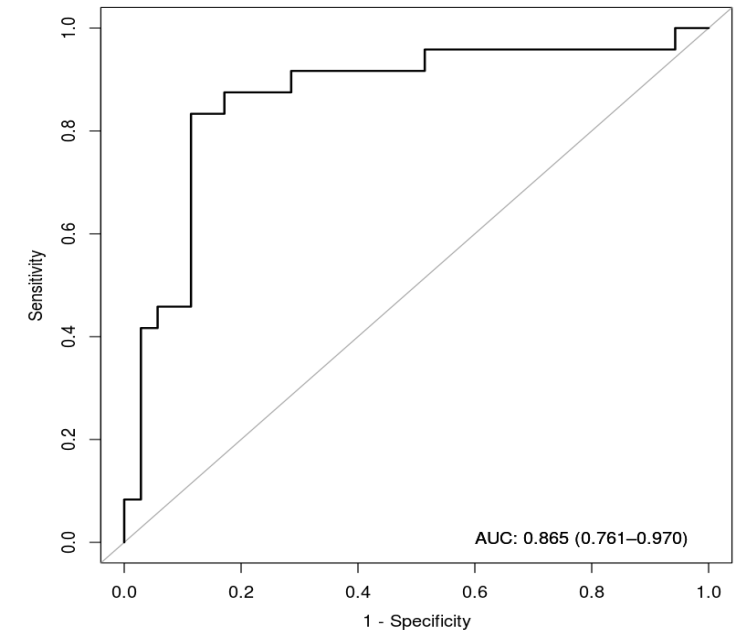


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Receiver-Operating-Characteristic (ROC) curve for Diagnosis of any-cause Acute Rejection and ABMR

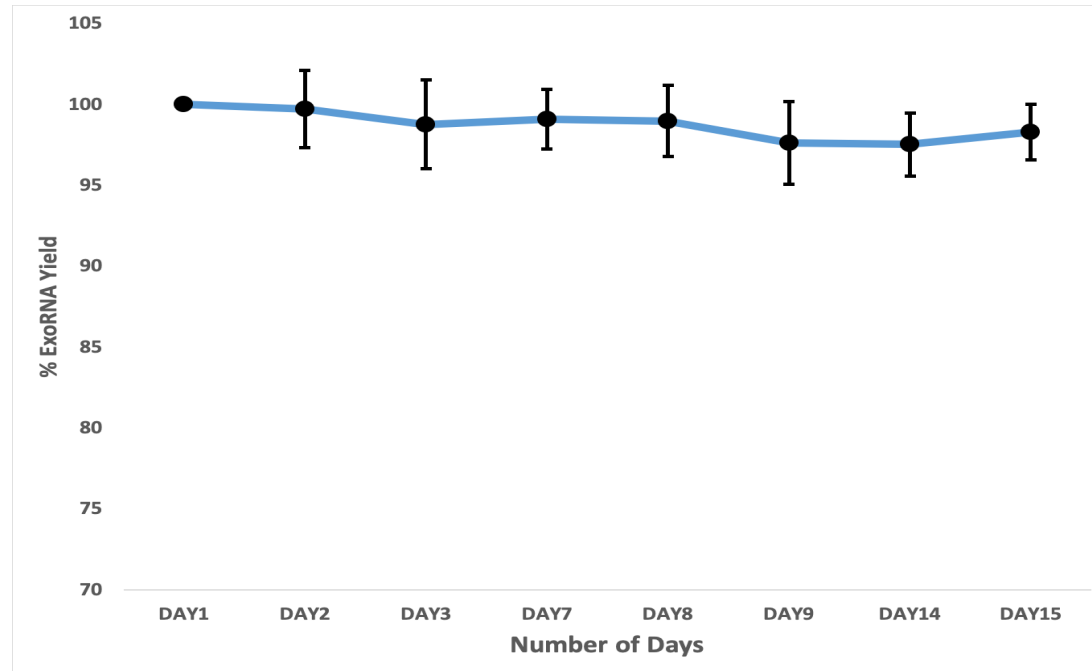


- Any cause rejection: Exosome RNA signature AUC = 0.90 (95% CI 0.84-0.96) vs eGFR AUC = 0.59 (95% CI 0.50-0.67).



ABMR discriminating RNA signature AUC 0.87 (95% CI 0.76-0.97).

Urine exosome RNA stability

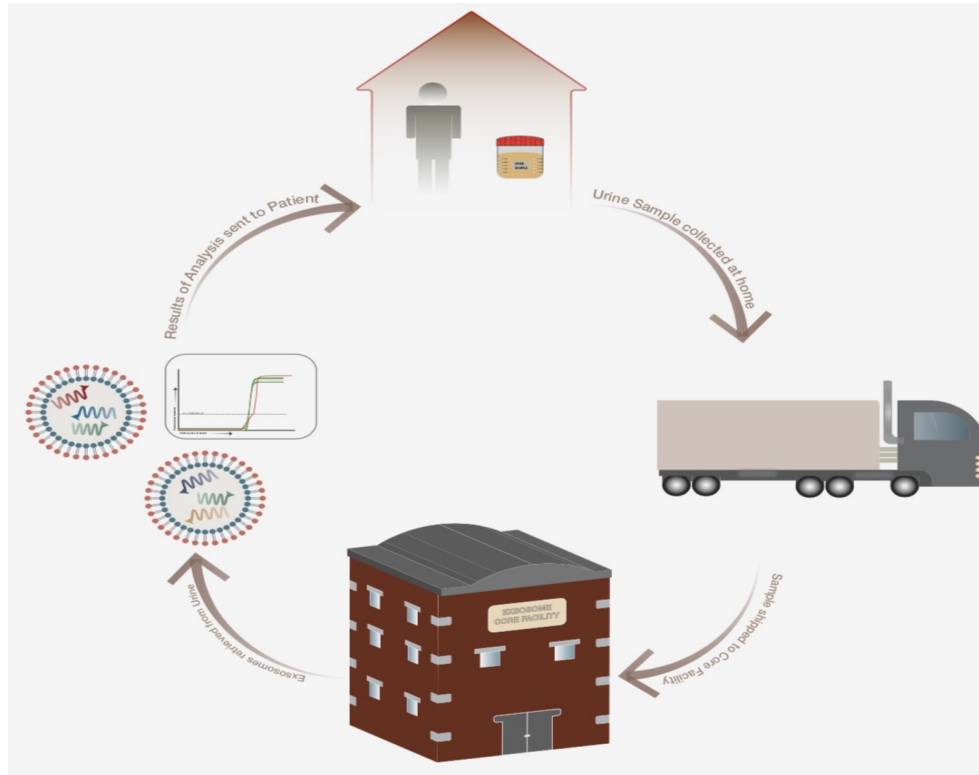


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Overview of the sample handling

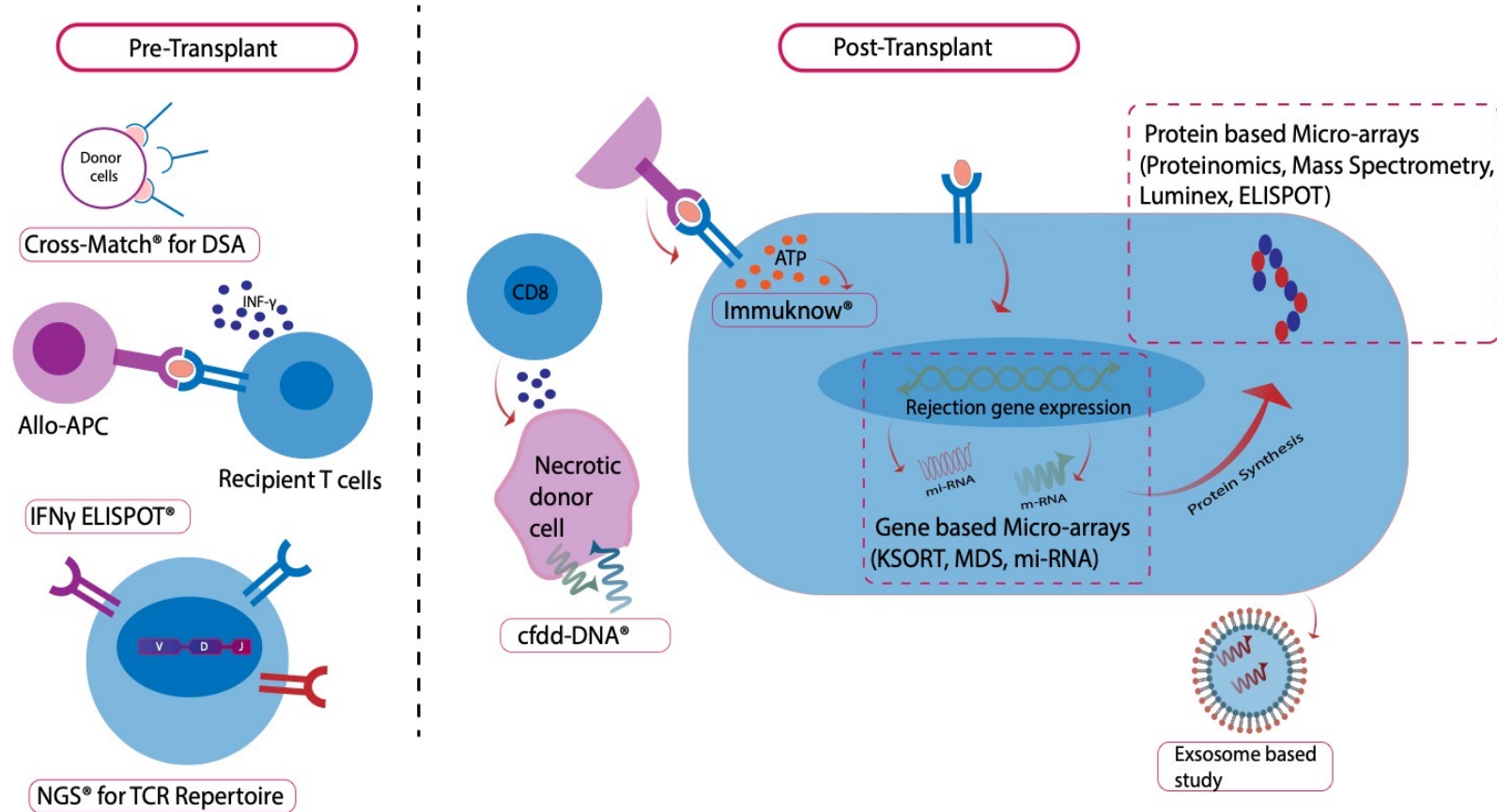


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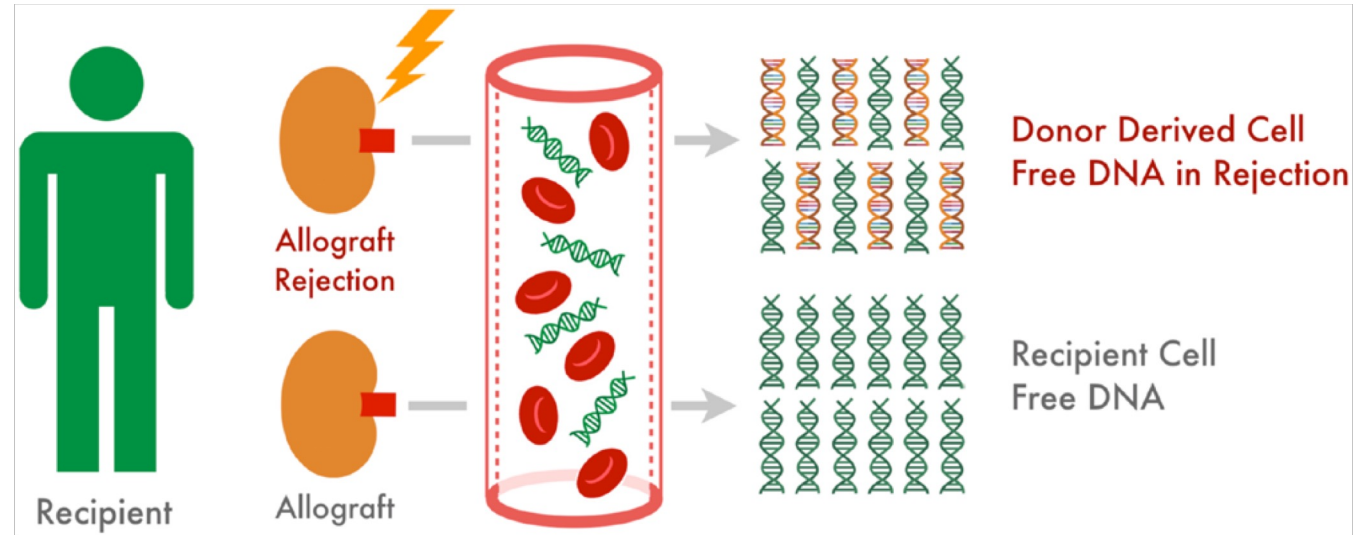
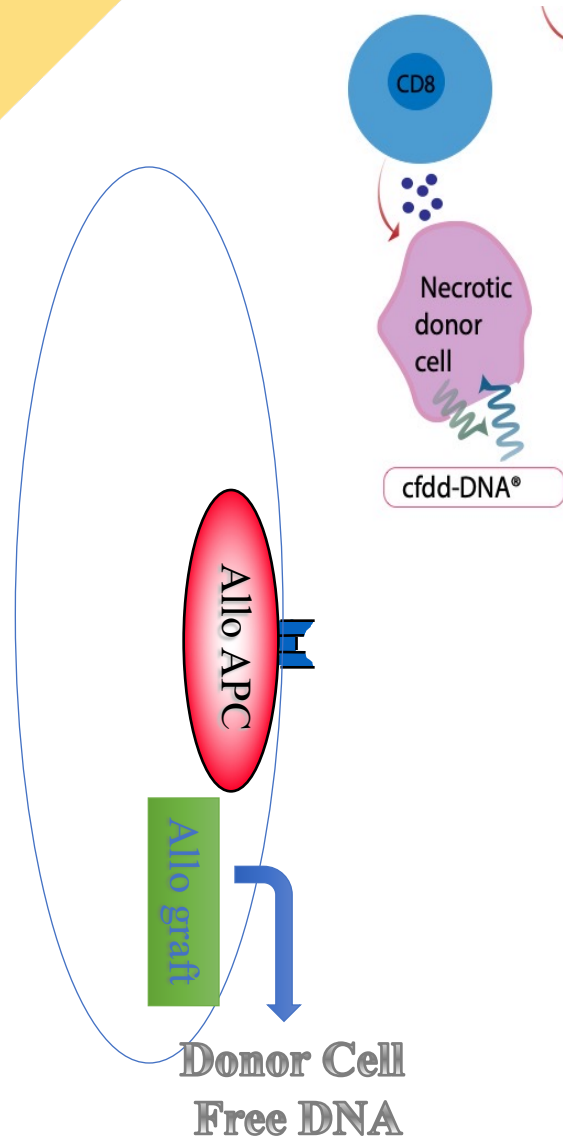


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Explored biomarkers in kidney transplantation

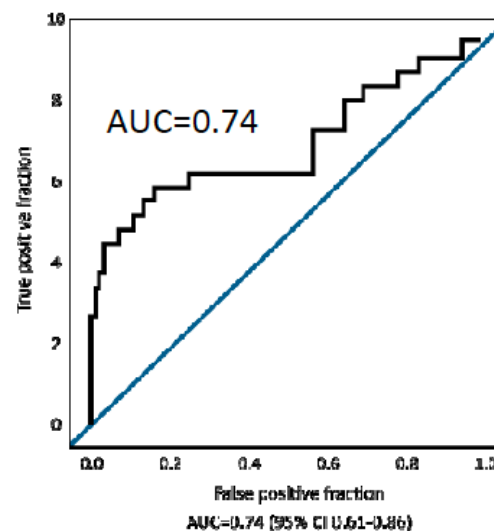
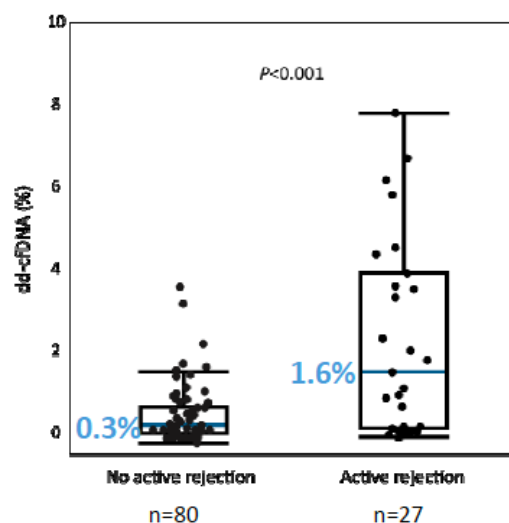
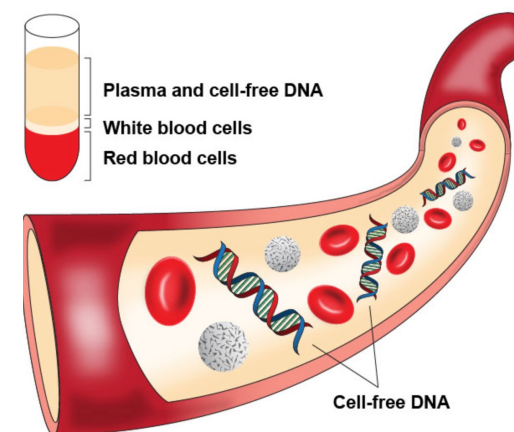


Clinically Available Biomarkers: Donor-derived Cell Free DNA



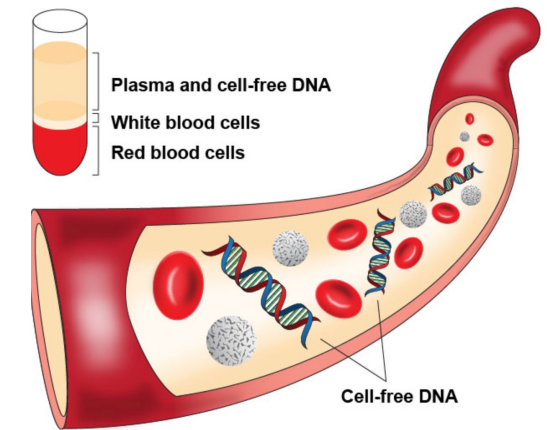
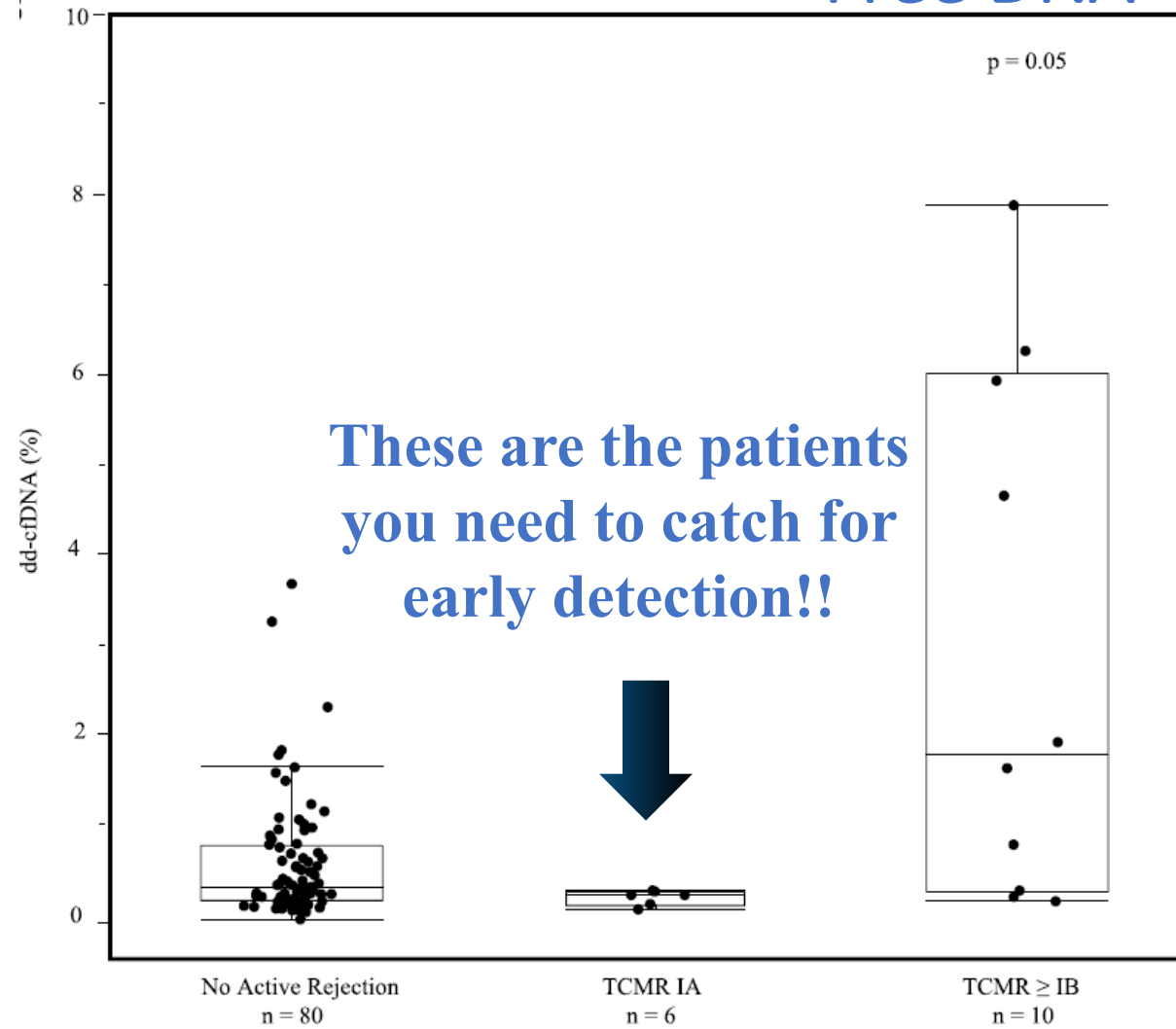
Clinically Available Biomarkers: Donor-derived Cell Free DNA

- DART study, Bloom et al, J Am Soc Nephrol, 28:2221-2232, 2017



Performance metric	AlloSure test performance at 1% threshold
ROC/AUC	0.74 (95% CI 0.61-0.86)
Sensitivity	85%
Specificity	59%
NPV	84%
PPV	61%

Clinically Available Biomarkers: Donor-derived Cell Free DNA

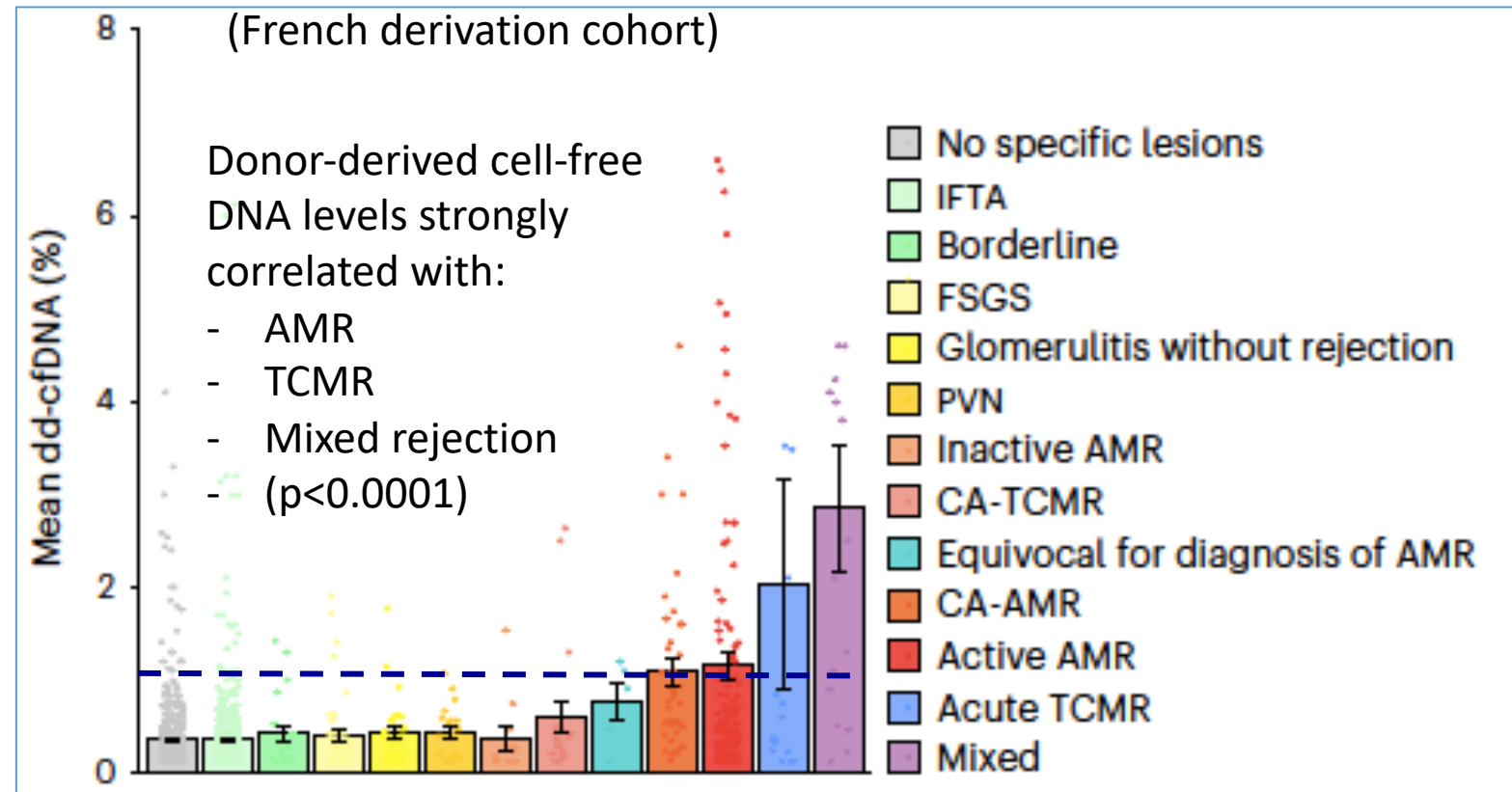


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Cell-free DNA for the detection of kidney allograft rejection

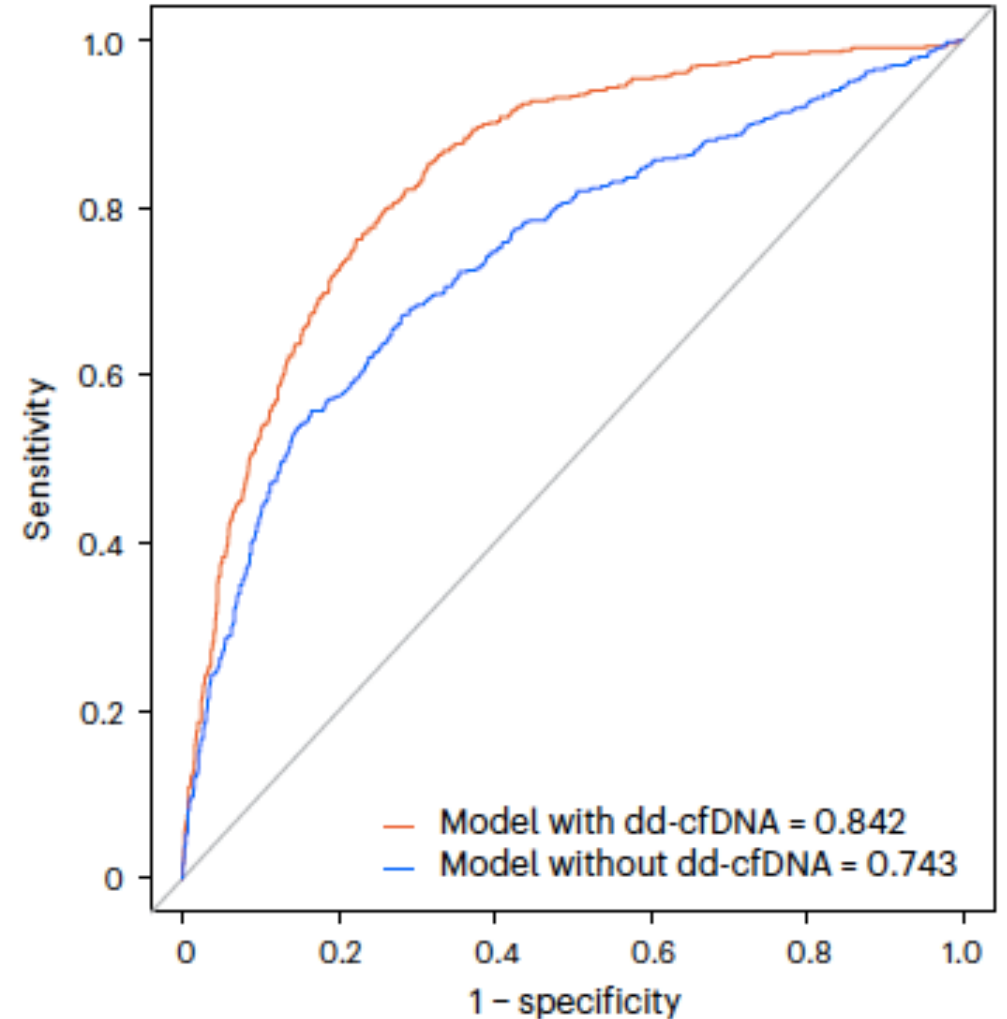
2,882 kidney tx recipients:

- 14 European and US Transplant centers
- An observational population-based study



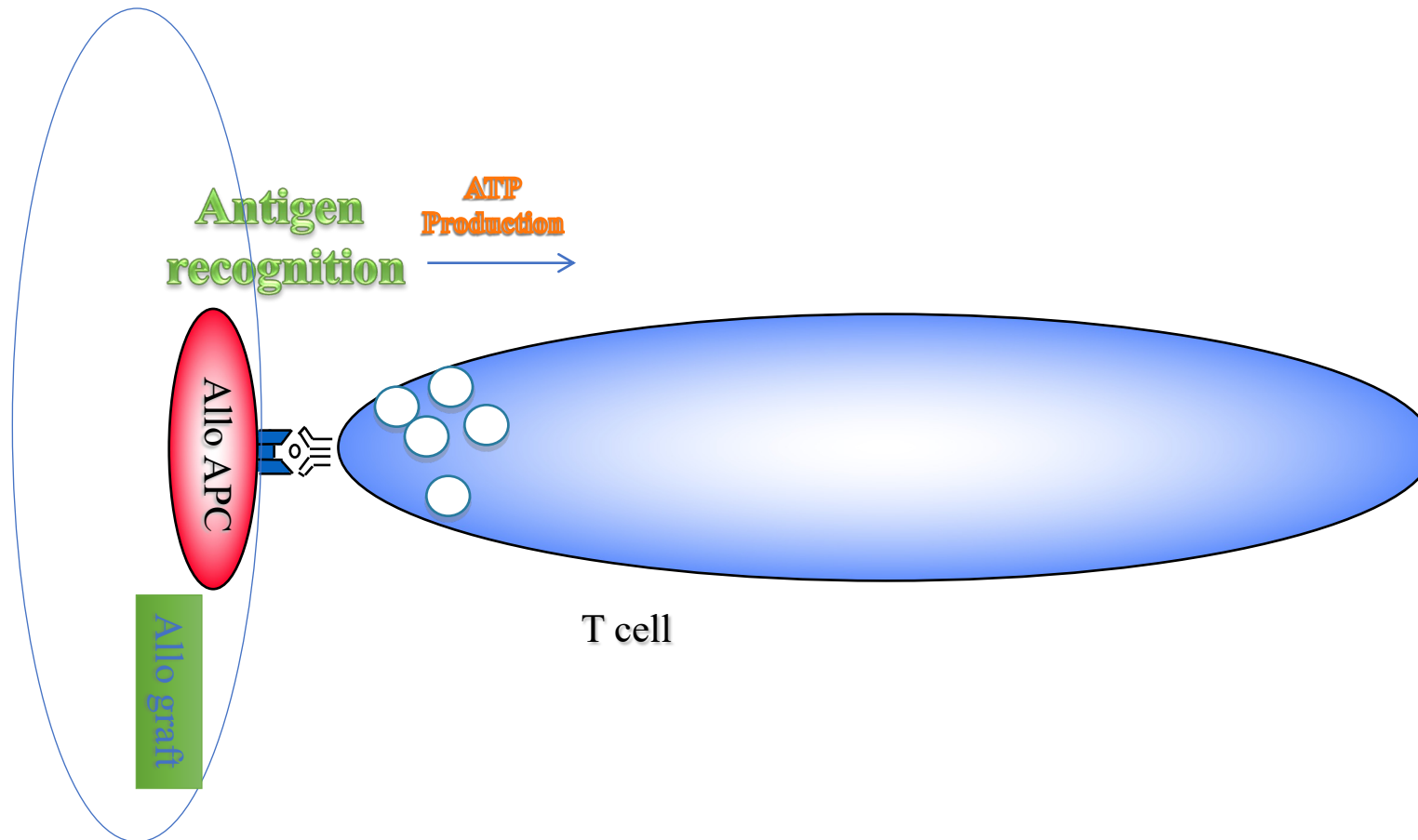
Cell-free DNA for the detection of kidney allograft rejection

Combining **dd-cfDNA** with **standard of care assessments** (eGFR, proteinuria, anti-HLA DSA, previous episode of rejection, kidney graft instability) improves ability to predict rejection
AUC **0.842** vs **0.743**

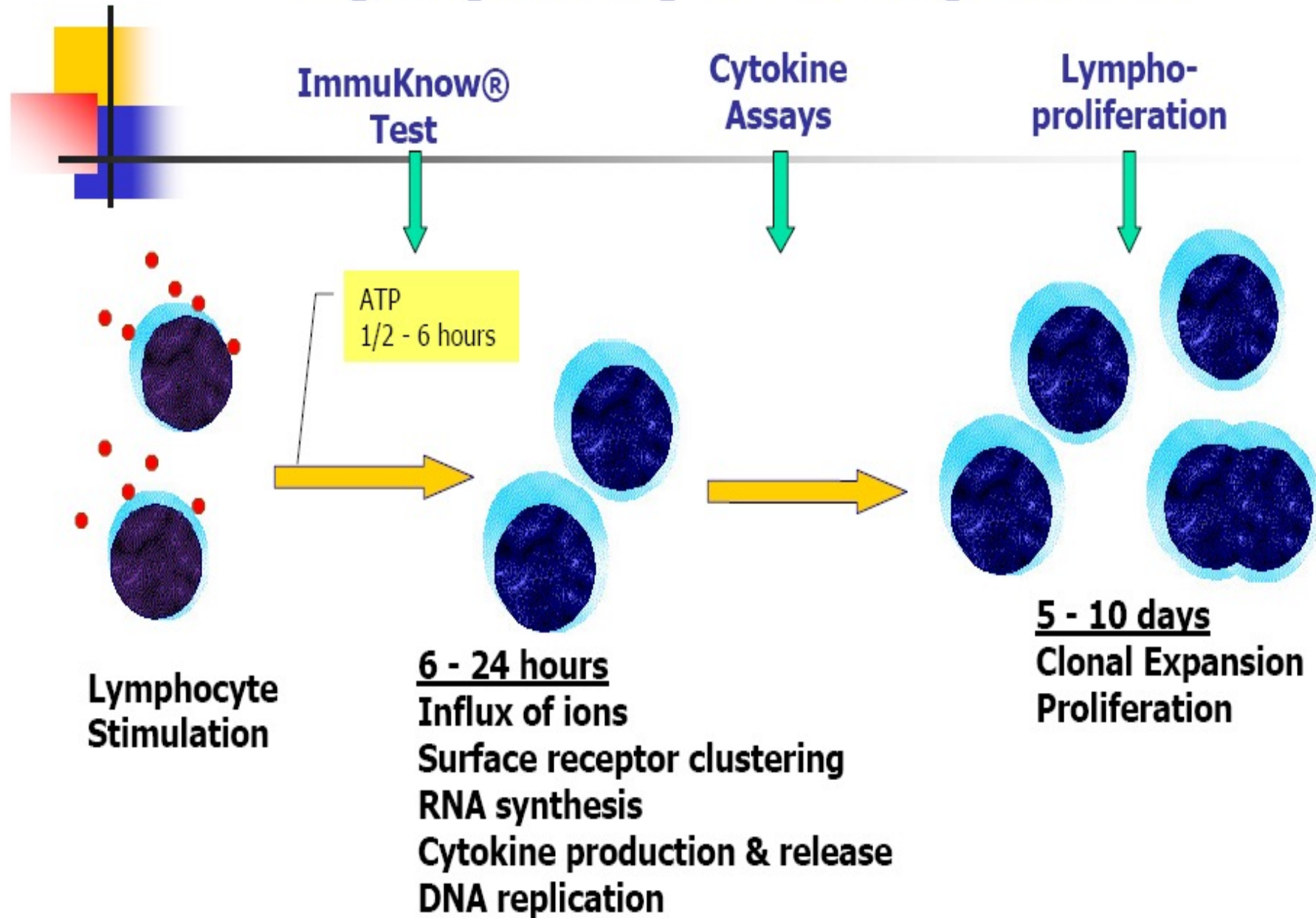


Clinically Available Biomarkers:

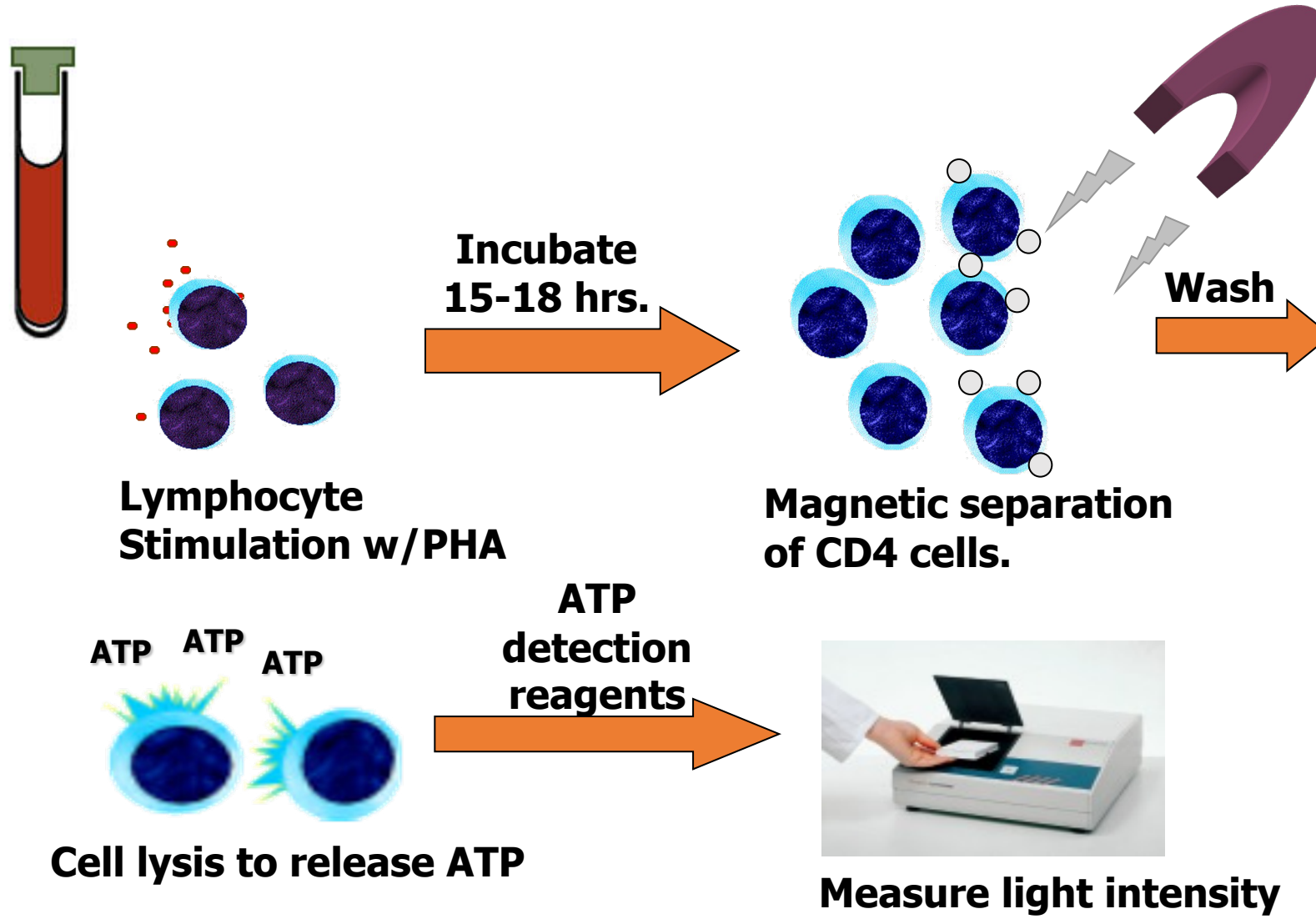
ImmuKnow



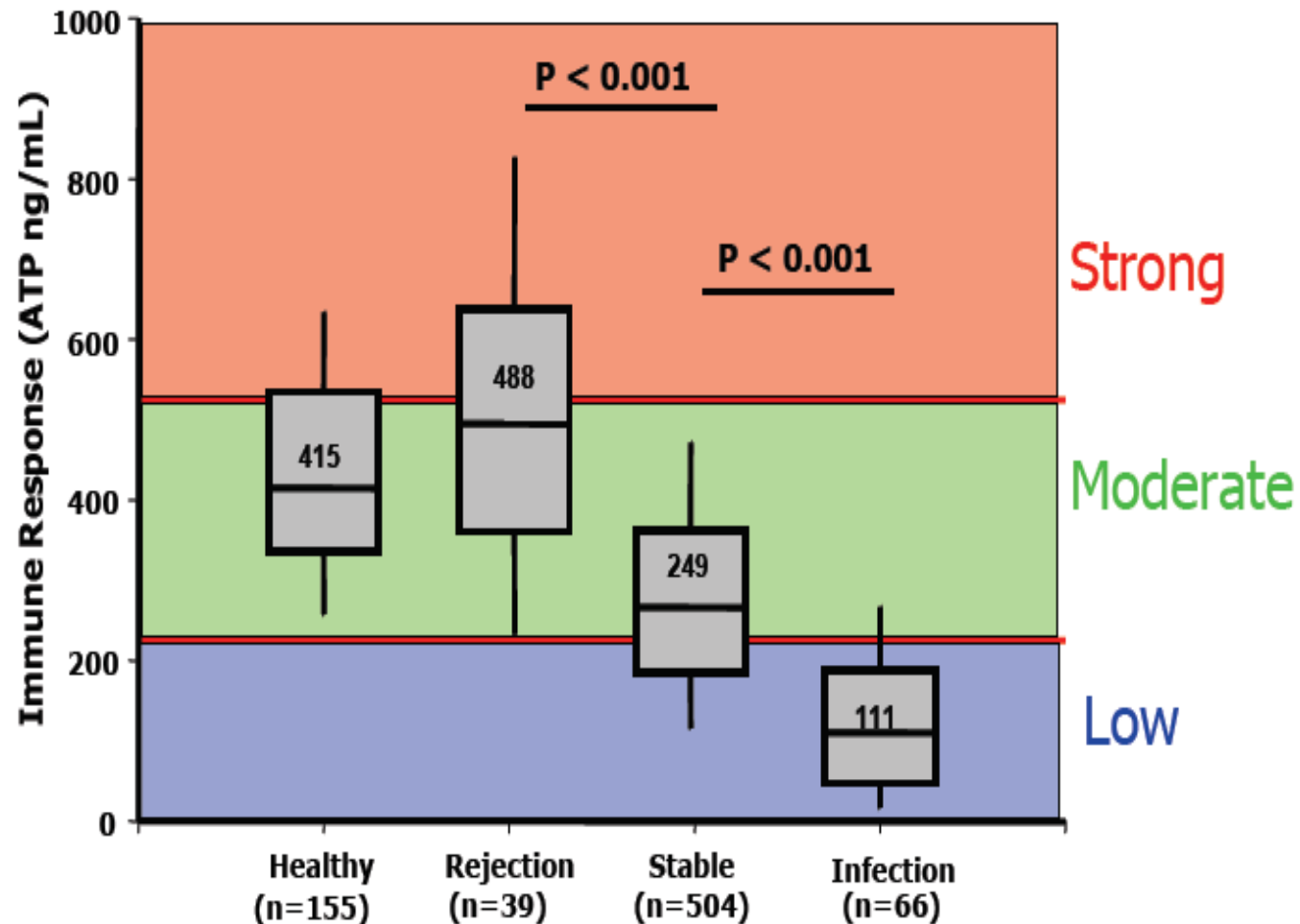
Lymphocyte Response



ImmuKnow™ Cell Function Test

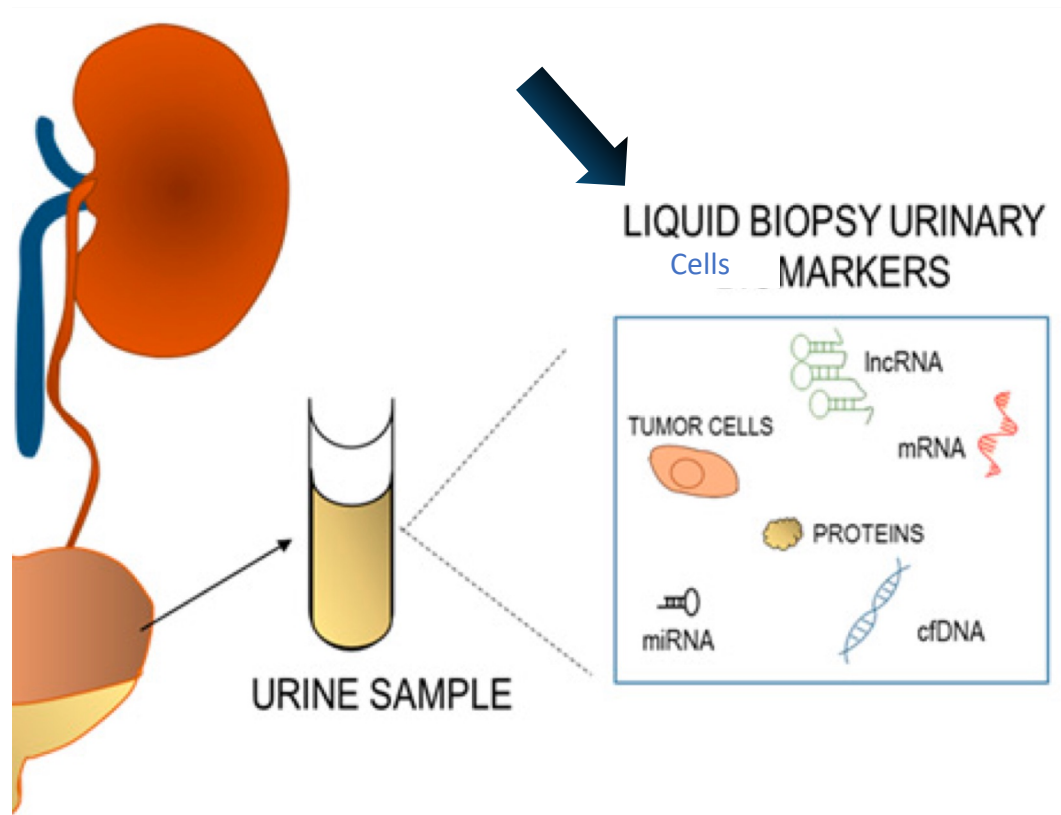


Immune Function Correlates With Clinical Outcomes



Multicenter Studies: NIDDK, UCLA, JHU, UPMC, NZTI, LifeLink, UAB, UMD, INOVA, UTMB

mRNA in Urinary Cells.



Li B et al. N Engl J Med 2001;344:947-954.
Suthanthiran M et al. N Engl J Med 2013;369:20-31.

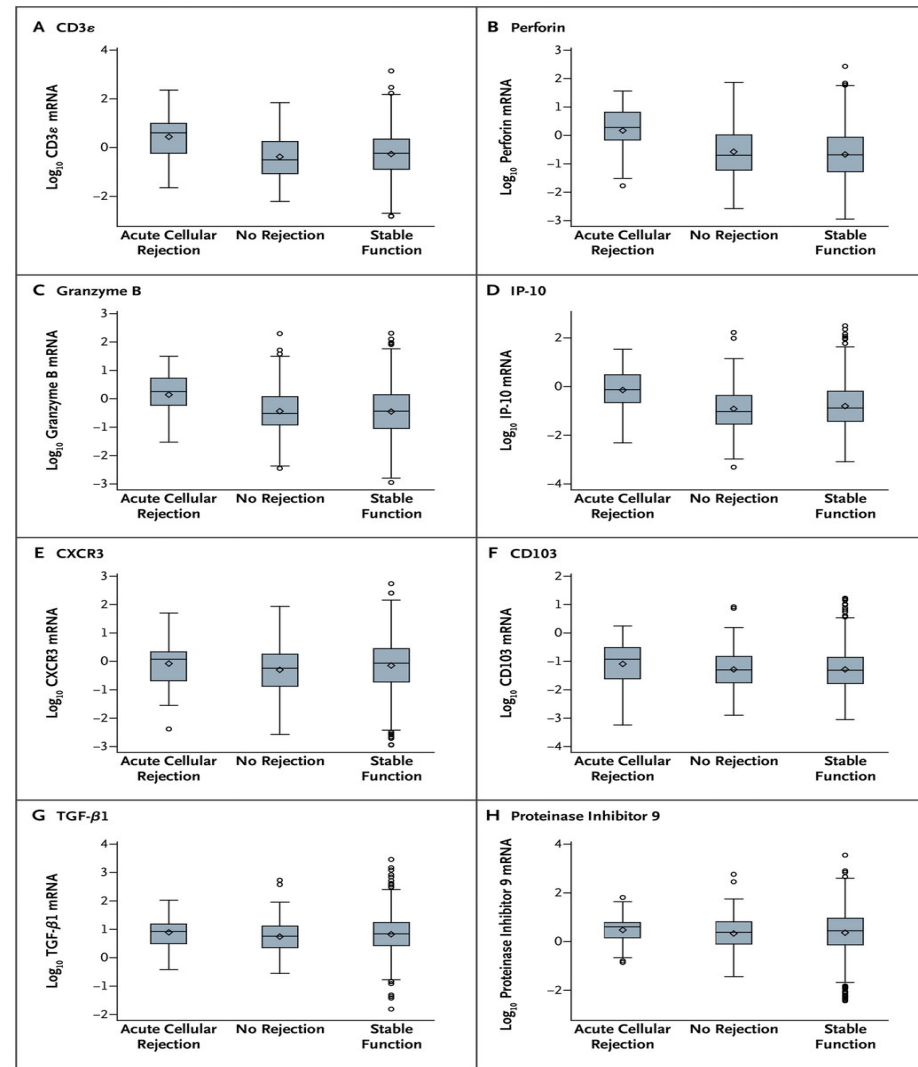


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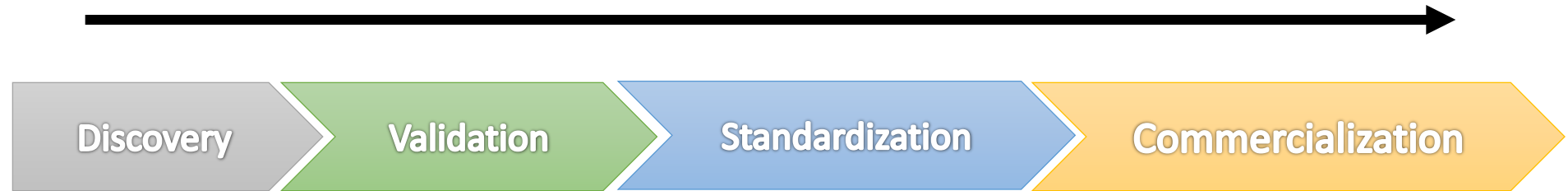
Levels of mRNA in Urinary Cells.



- Prospective collection
- 4300 urine specimens from 485 kidney-graft recipients
- Day 3 through month 12 after transplantation.
- CD3ε, IP-10 and 18S rRNA
 - 79% sensitivity and 78% specificity
 - [AUC], 0.85

Suthanthiran M et al. N Engl J Med 2013;369:20-31.

Phases of Biomarkers Discovery



- Targeted or non-targeted approaches
- High-throughput technologies
- Identify a panel

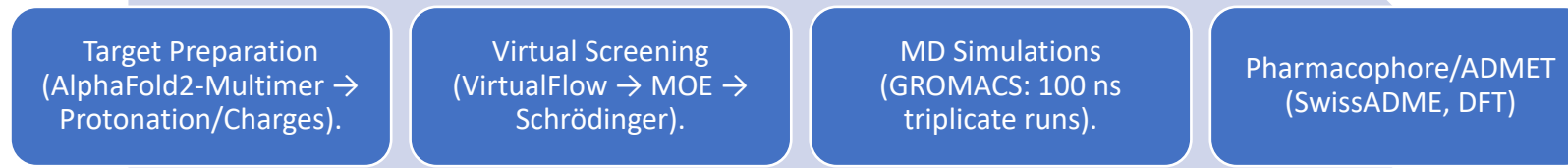
- Use independent samples
- Identify a refined set
- Prospective multicentral validation

- Laboratory equipment
- Reagents
- Can the test be reproduced in different laboratories

Compound 778 interaction with CD74



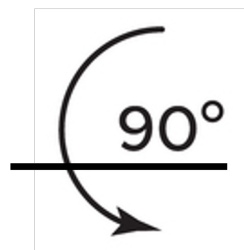
Computational Workflow



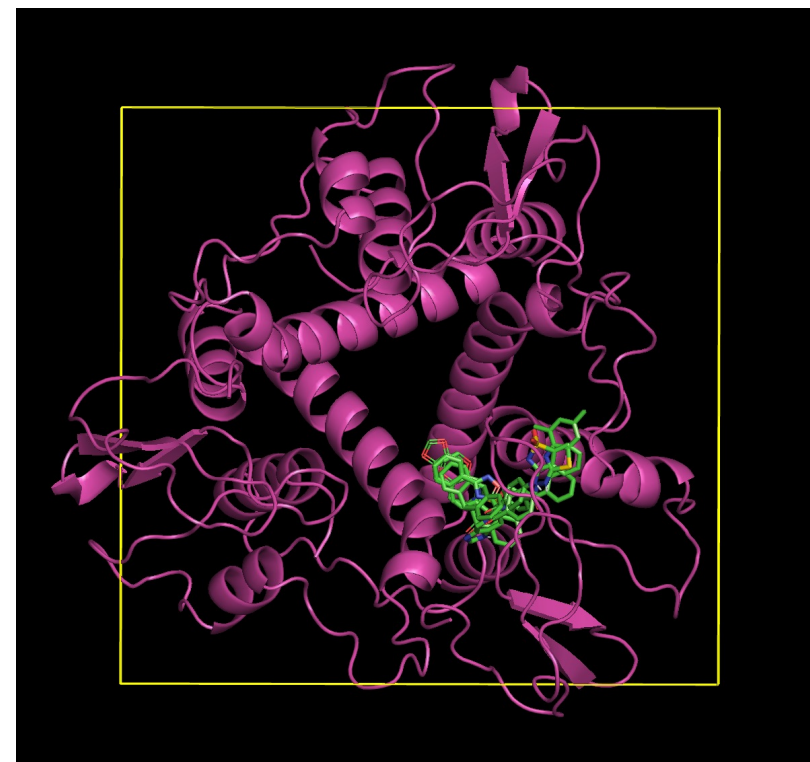
side view



Docking box



top view



Screening using ELISA based assay:

Top 100 candidate compound were synthesized and screened.

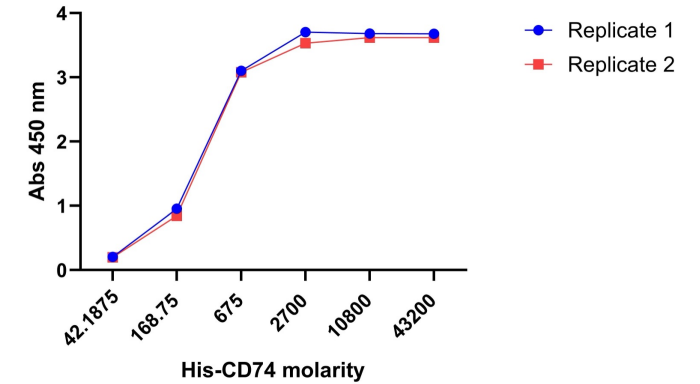
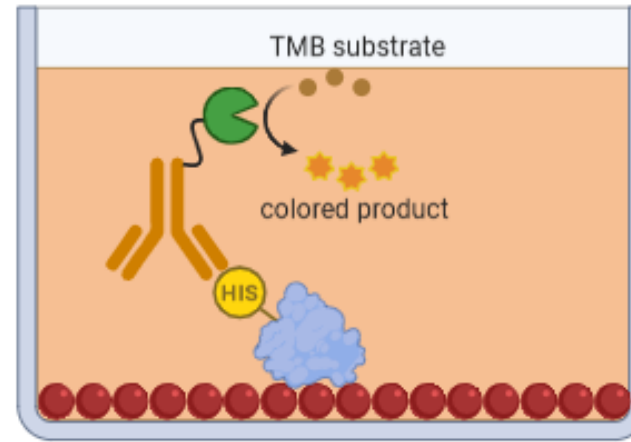
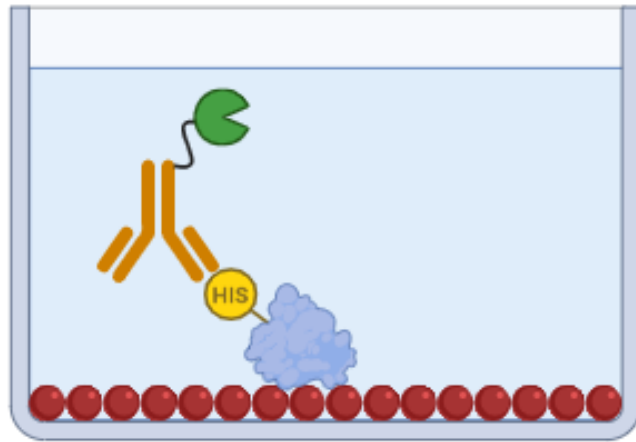
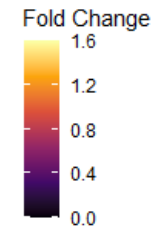


Plate 1

A	2.90	0.83	3.24	0.38	0.52	0.38	0.13	0.24	0.14	0.17
B	0.17	0.68	0.25	0.04	1.67	0.00	0.13	0.30	0.22	0.23
C	1.03	0.14	0.69	0.09	0.16	0.08	0.23	0.19	0.25	0.27
D	0.43	0.14	0.09	0.07	0.99	0.00	0.42	0.13	0.14	0.23
E	0.82	0.15	0.09	0.14	0.19	0.05	0.11	2.06	0.69	0.49
F	0.15	0.13	1.89	0.62	0.07	0.09	0.13	0.14	0.35	0.22
G	0.57	0.20	0.72	0.18	0.07	0.13	0.18	0.19	0.27	0.35
H	0.78	0.14	0.03	0.19	0.12	0.07	0.13	0.21	0.21	0.22
	2	3	4	5	6	7	8	9	10	11

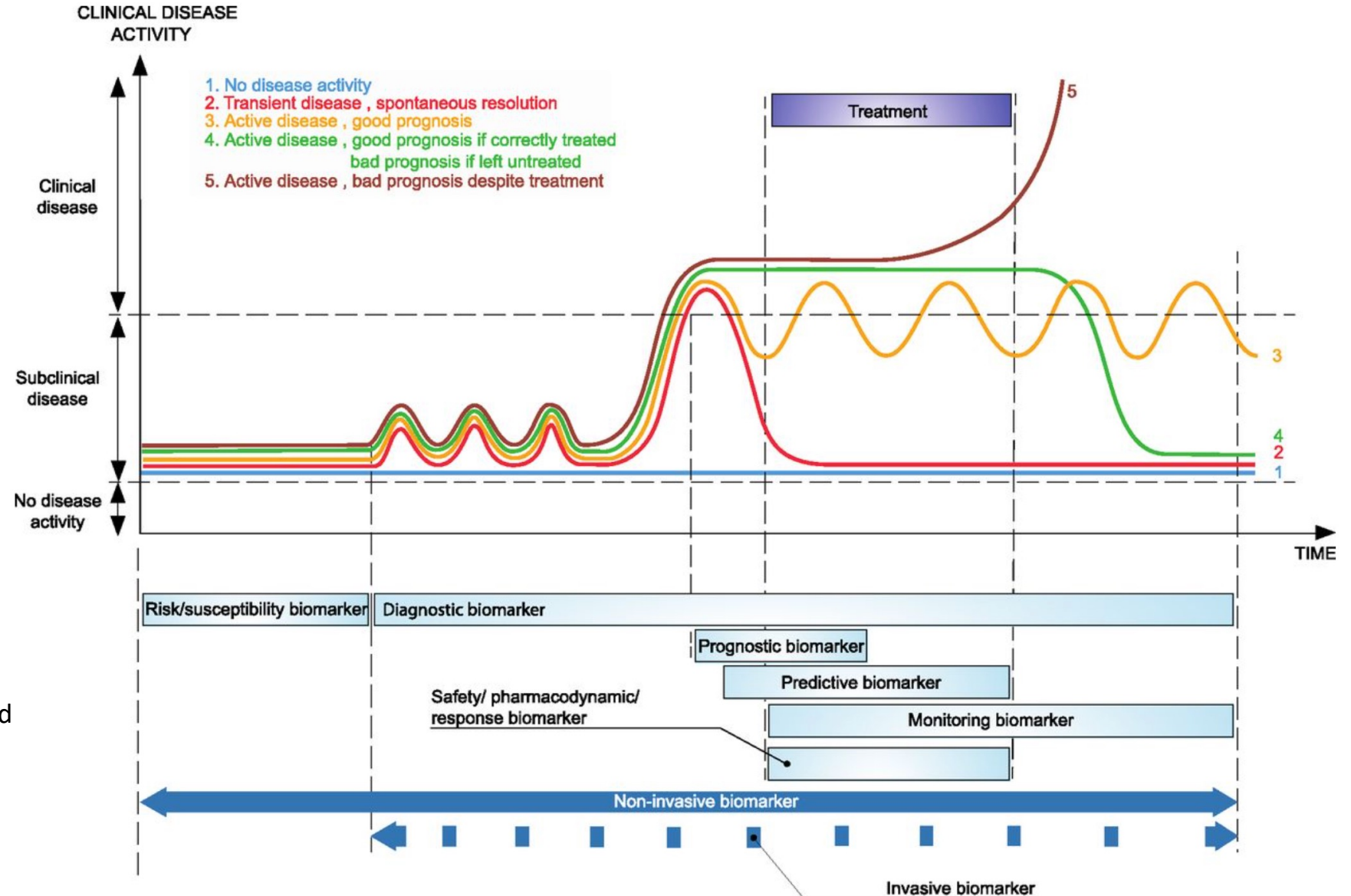
Plate 2

A	0.07	0.03	0.05
B	0.12	0.36	0.15
C	0.19	0.07	0.08
D	0.38	0.13	0.52
E	0.32	0.56	2.42
F	0.76	1.40	0.02
G	0.01	0.28	0.48
H	0.17	0.36	0.14
	2	3	4



Biomarkers subtypes

- **Prognostic biomarkers:**
 - predict clinical outcome regardless of treatment
- **Predictive biomarkers:**
 - Change in response to treatment
- **Surrogate end points:**
 - Substitute for a clinical end point.



Long-term outcomes following acute rejection in kidney transplant recipients



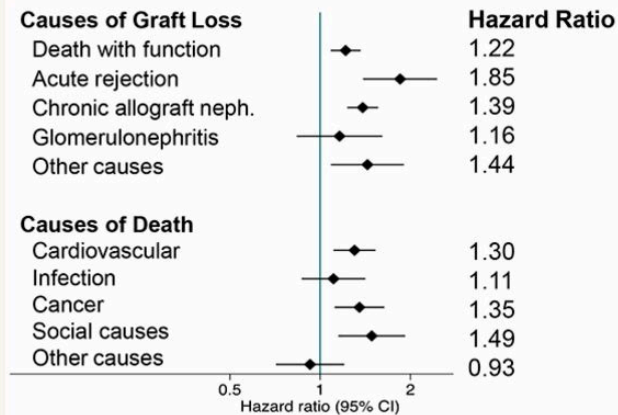
13614 KTRs 1997-2017
2906 with early acute rejection
(AR in 1st 6mth)

Comparison of AR vs no AR:

- Graft survival
 - Causes of graft loss
- Patient survival
 - Causes of death

Models adjusted for era, donor, recipient, immune risk and DGF

Association between early AR and late outcomes for KTRs



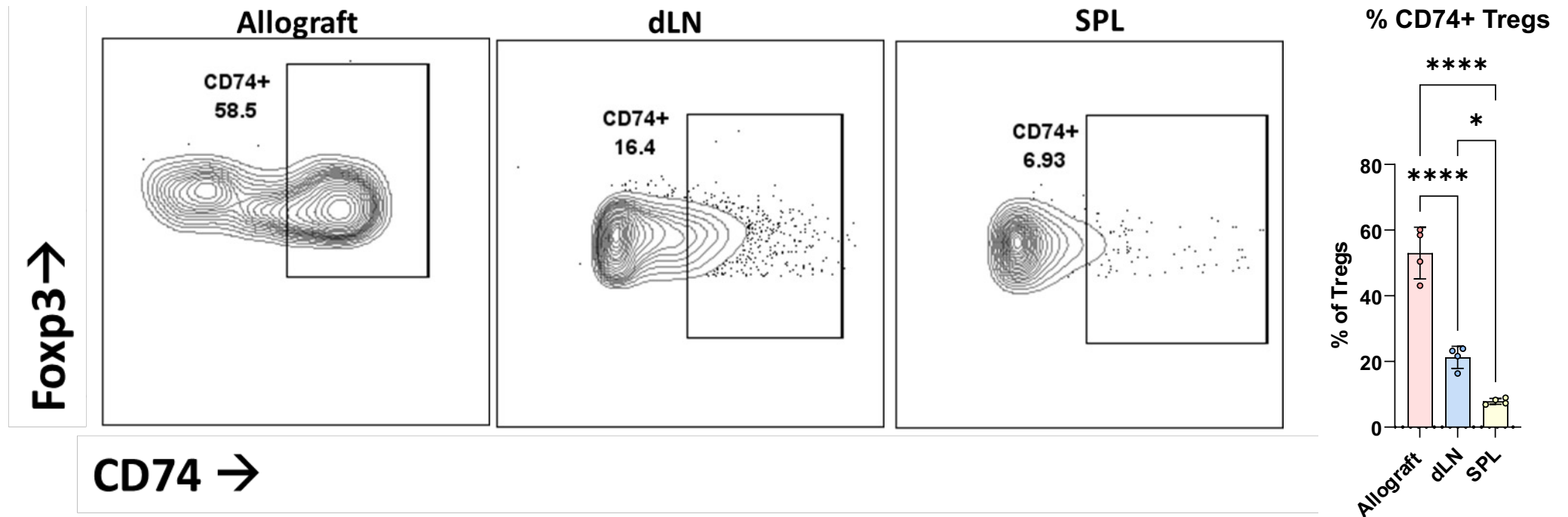
KTRs with early AR are at increased risks of death, from CV disease and cancer, and graft failure, from chronic allograft nephropathy and late AR.

doi: 10.1681/ASN.2018111101

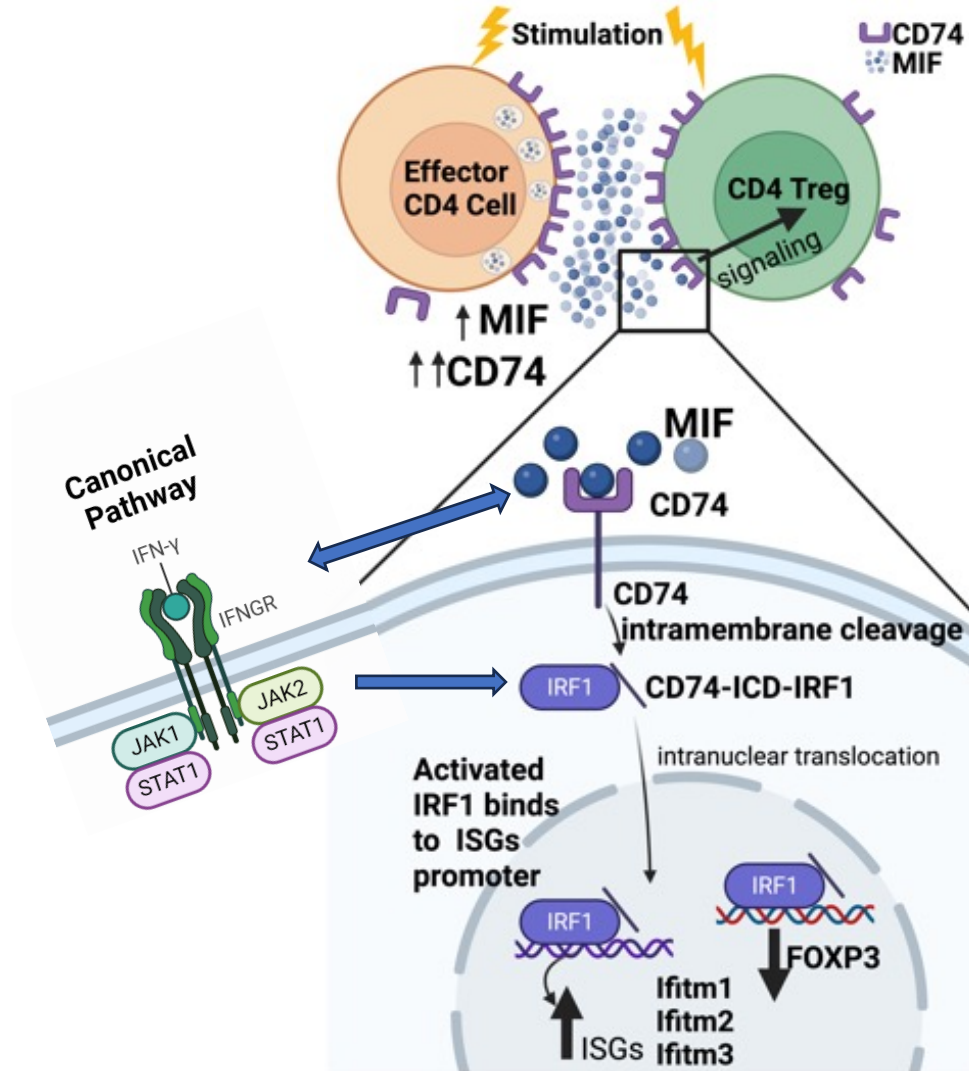
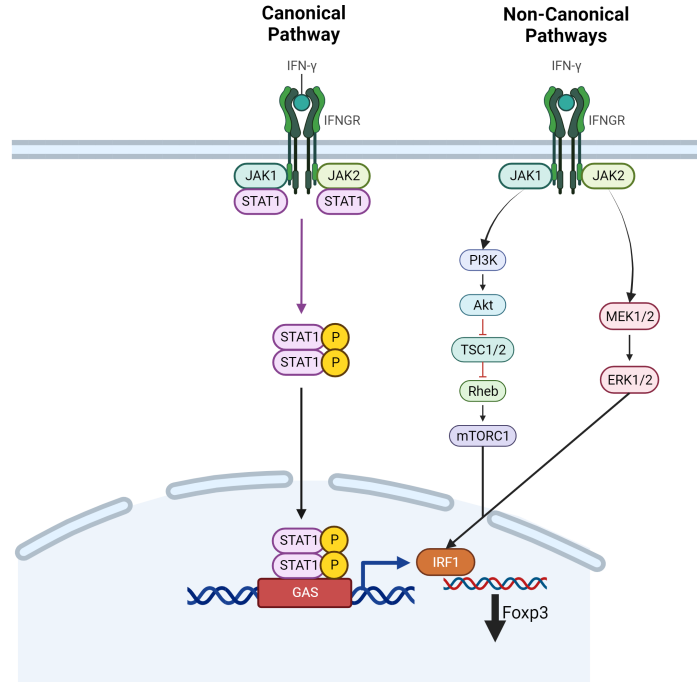
Philip A. Clayton et al. JASN 2019;30:1697-1707

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Frequency of CD74+ Tregs Increases in Allograft and Draining Lymph Node



MIF-CD74 pathway inhibits Tregs homeostasis, function and stability with potential collaboration from IFN γ



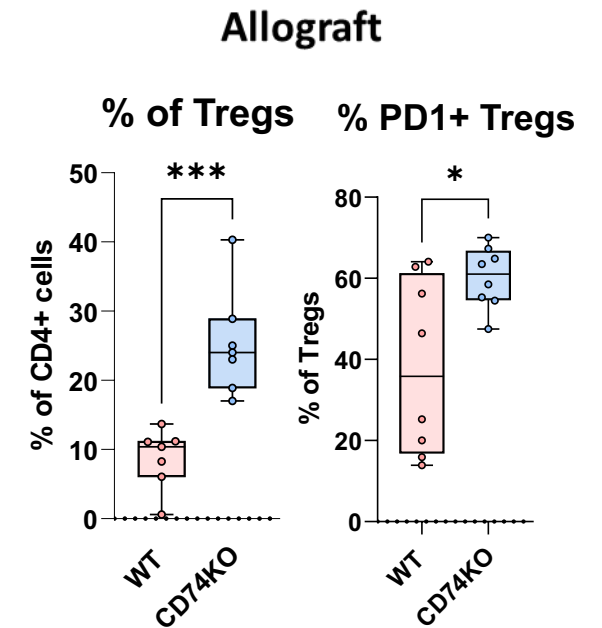
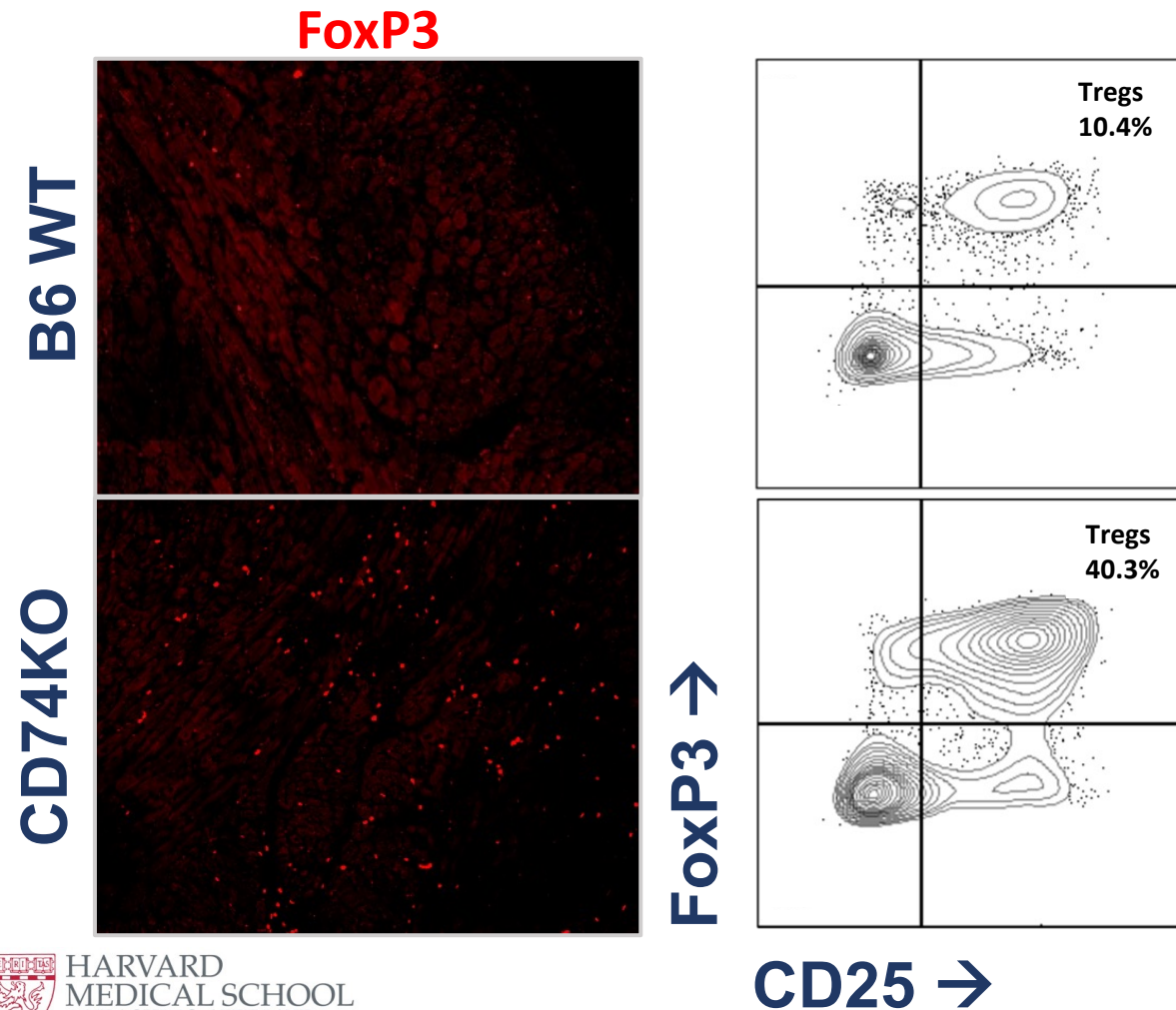
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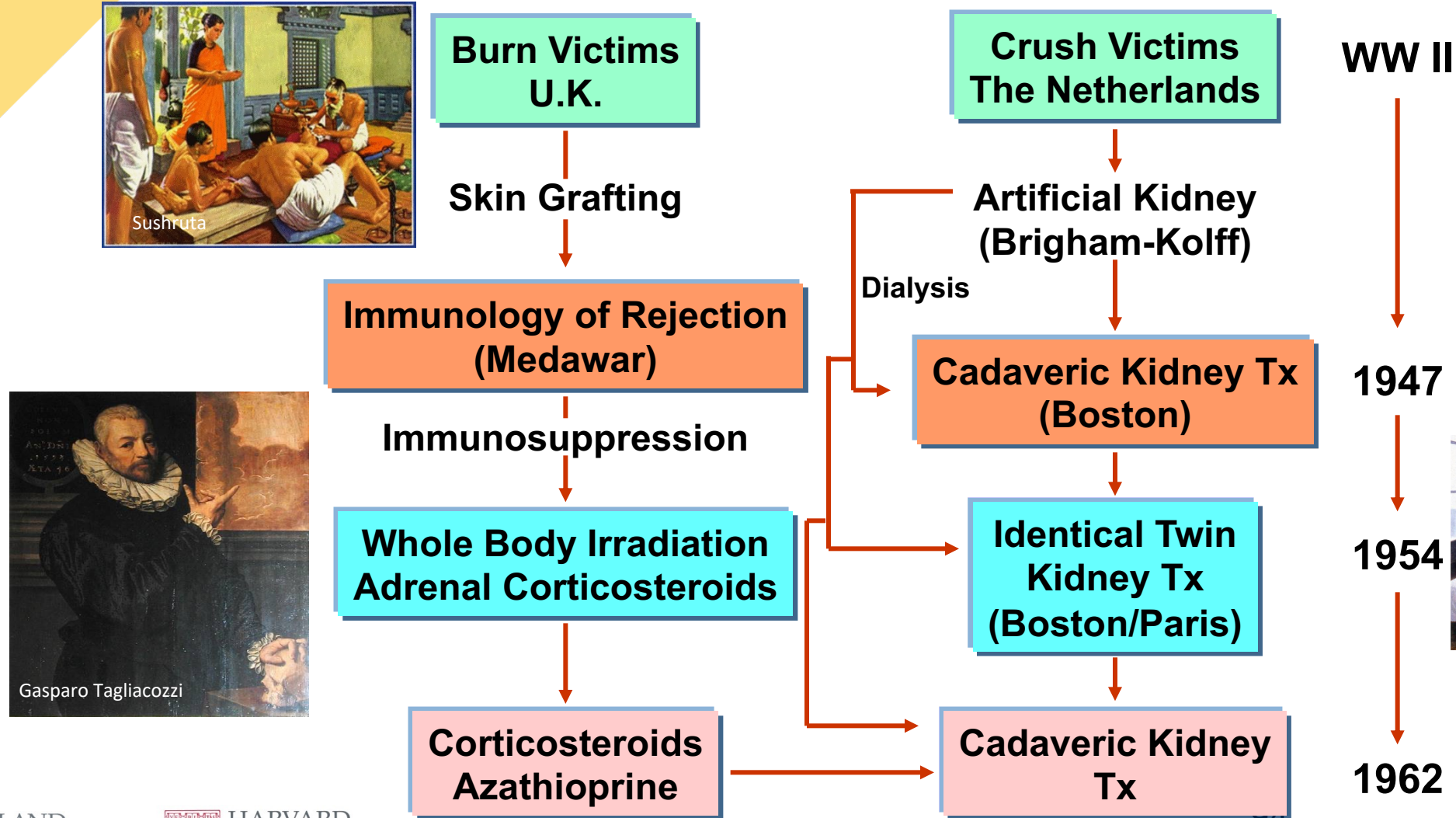
Unpublished data

CD74KO Recipient's Allograft Show Heightened Treg Infiltration



Unpublished data

Over 70 Years of Kidney Transplantation: Have We Changed the Paradigm?



Balancing Immunosuppression, Infection And Malignancy

Too Much

- *Infection*
- *Malignancy*

Too Little

- *Allograft Rejection*

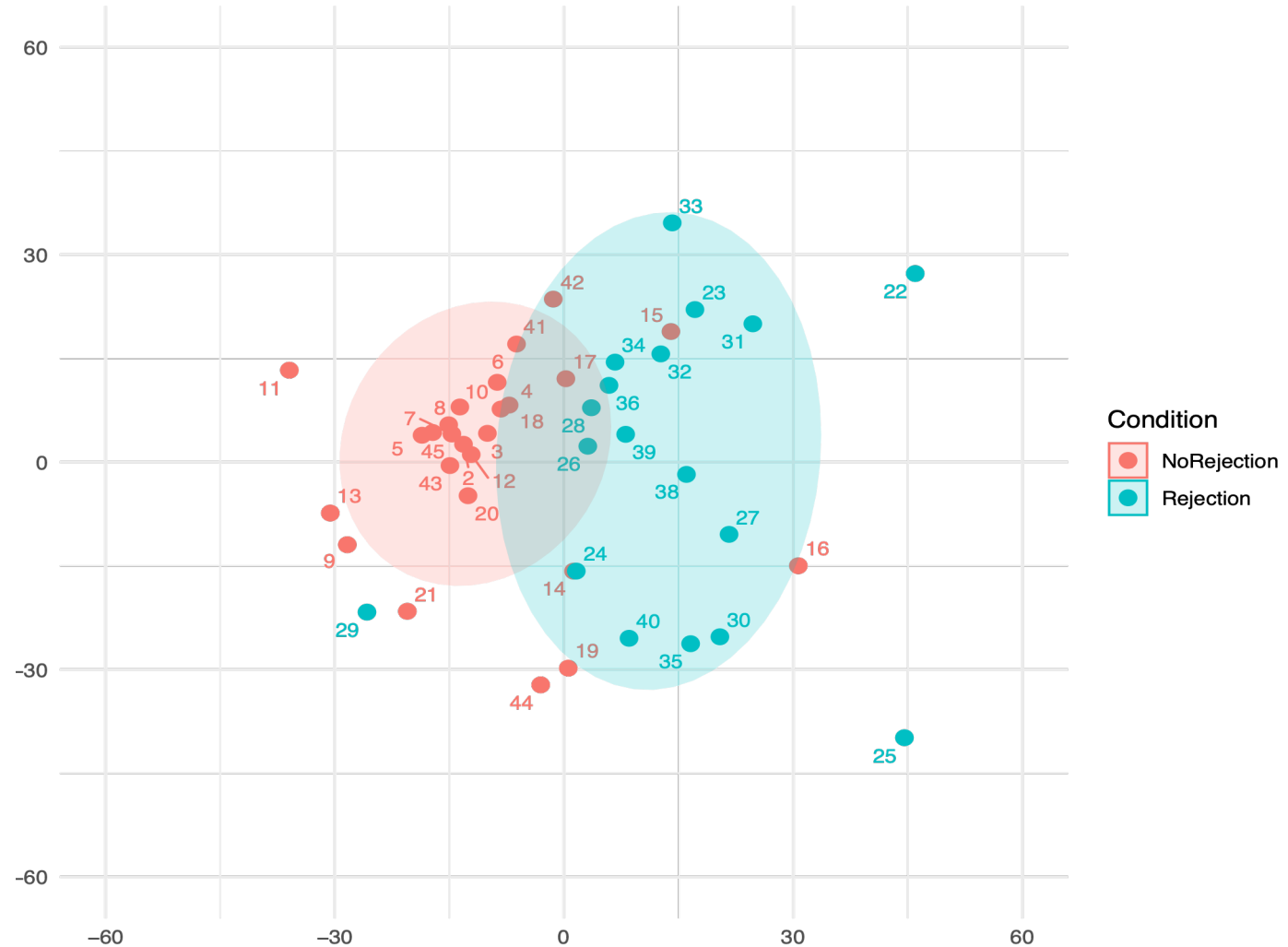


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PCA analysis of the RNA sequencing data show a distinct clustering of rejection and non-rejection patients



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To raise or not to raise!!!

32 yo female with history of ESRD 2/2 MPGN type 1 and chronic immune complex GN with long history of treatment with IS, s/p LRKTx in 2017 cw EBV-negative PTLD, DLBCL type.

Completed 4 does of rituximab, followed by R-CHOP and she completed 4 cycles through 10/16/24.

PET CT 11/18/2024 No evidence of FDG avid disease.

Cr stable at baseline, 0.85 UPCR 0.11

On TAC 0.5 mg twice daily, level 5.3 and on prednisone 5 mg

-Discussed IS regimen option to switch from Tac to mTOR inh

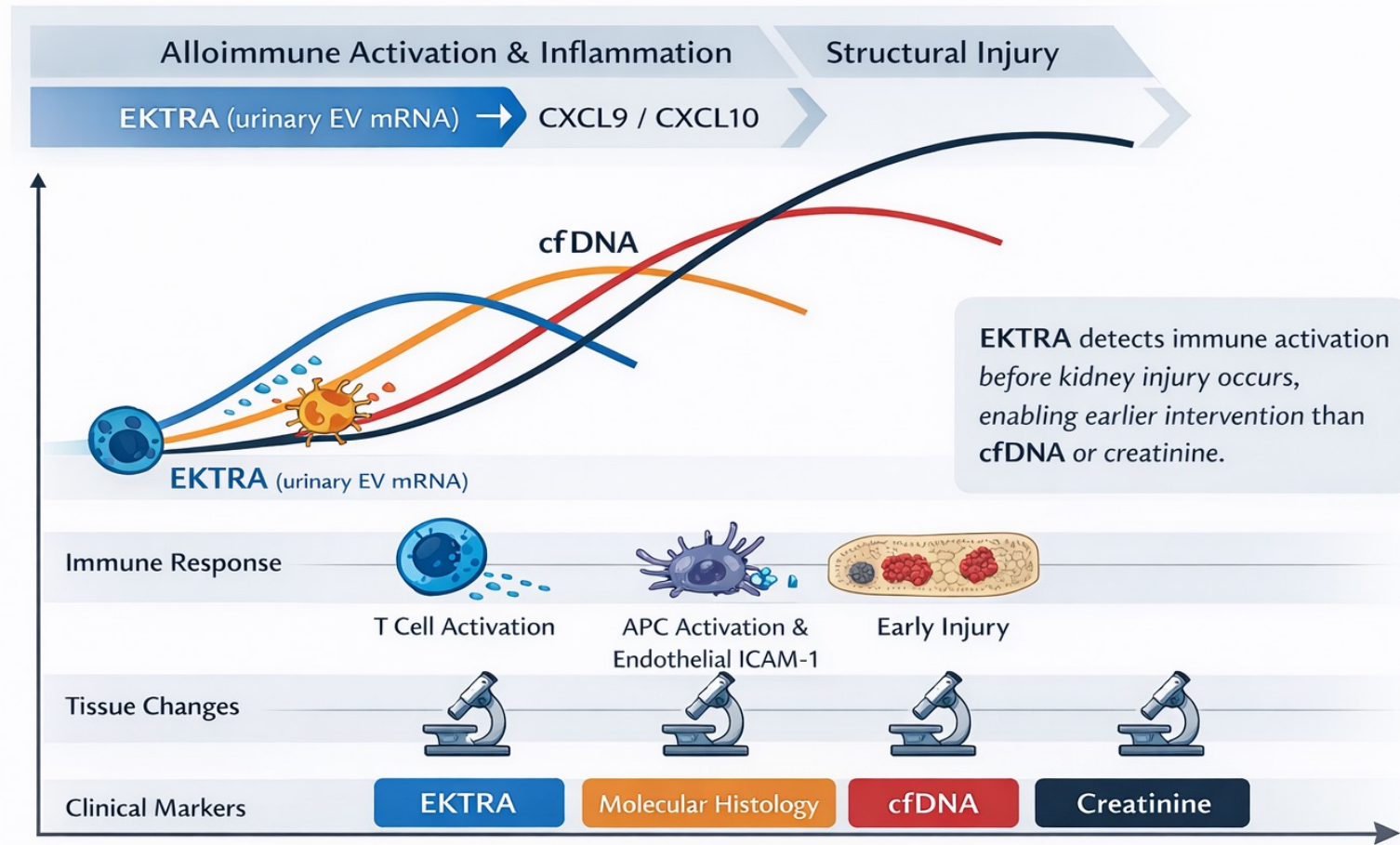
-Patient anxious about her kidney function long-term. Should we reoptimize IS?

Lessons learned at BWH: EKTRA in the Clinic

- Excellent rule out test
- Stable kidney function and no proteinuria with EKTRA positive-> Many cases of ABMR and ACR from borderline to 2A
- cfDNA negative but EKTRA positive: Few cases showing biopsy with active disease from interstitial inflammation to ACR IB and partially treated ABMR.
- Patients with history of ESRD secondary to IgA nephropathy with positive EKTRA post transplant-> IgA nephropathy recurrence even in the absence of proteinuria and hematuria.
- EKTRA positive but biopsy normal: High Risk patients.
- Limitations: Preemptive Transplantation, urine infections...

Inflammation Precedes Injury

Inflammation Precedes Injury in Kidney Transplantation



Building a Complete Translational Pipeline

Connecting human Findings to advanced therapeutic development



Bridging the Gap

Connecting human sample findings to small animal models and non-human primates.



Therapeutic Platforms

Developing in-house or partnered platforms for biologics, gene therapies, and small molecules.



AI-Powered Discovery

Harnessing AI for virtual drug screening and drug repurposing.