Η διαφαινόμενη γενετική θεραπευτική της πολυκυστικής νόσου των νεφρών

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Νεφρολόγος

Γεν. Νοσοκομείο Αθηνών «Γ. Γεννηματάς»

TARGET-PKD

Διαφαινόμενη = Επερχόμενη

Study design of a global **Phase 3 trial** evaluating the efficacy and safety of Study design of a global Phase 3 trial evaluating **the efficacy and safety of farabursen, an anti-miR-17 oligonucleotide**, in patients with ADPKD

multicenter, randomized, double-blind, placebo-controlled trial

Approximately **95** ...across the two fixed dose groups

Πρώτη γενετική θεραπεία νεφρικού νοσήματος που φθάνει σε επίπεδο κλινικής μελέτης φάσης 3

The primary efficacy endpoints
log-transformed **ratio to baseline in TKV at Week 52** assessed at the pre-specified interim analysis, and **change in eGFR from baseline to Week 104** assessed at the final analysis

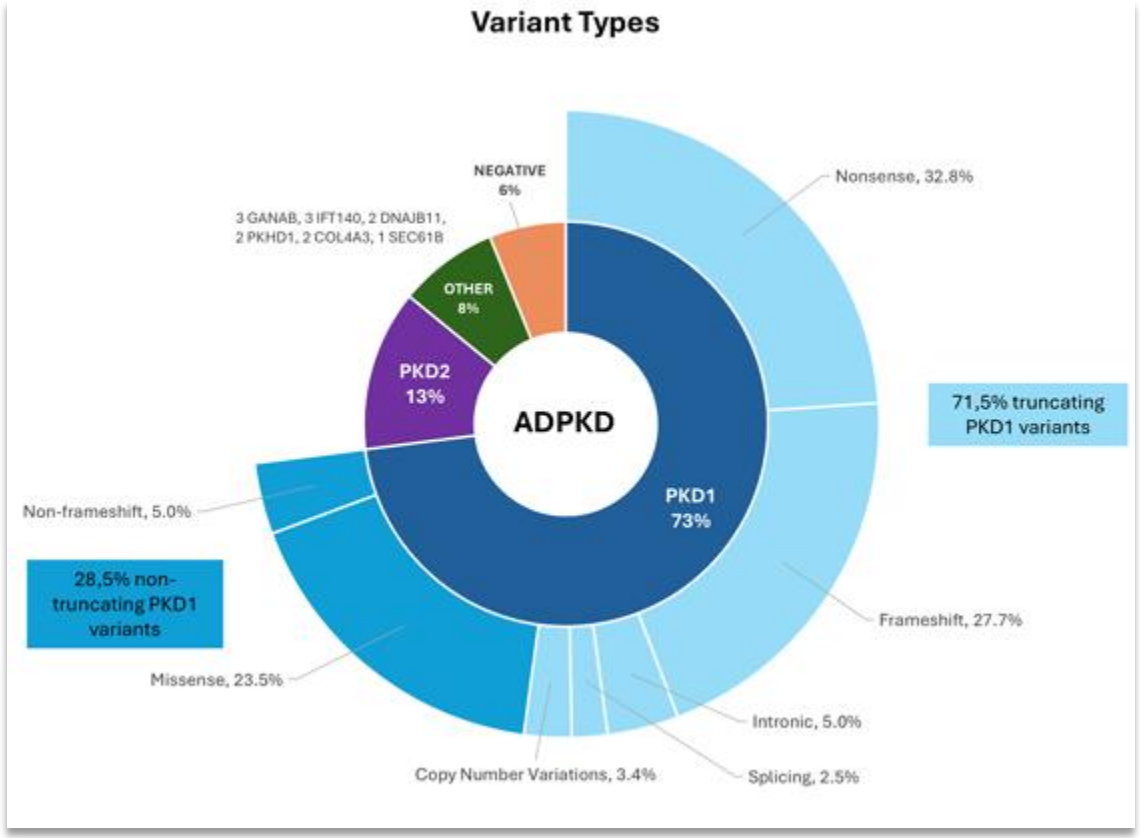
Conclusion Targeting **miR-17 is a promising novel therapeutic strategy for ADPKD** focusing on **increasing tissue availability of functional PC1 and PC2.**

Γιατί είναι αναγκαία (και επαρκής) η γενετική θεραπευτική στην Πολυκυστική νόσο των νεφρών ?

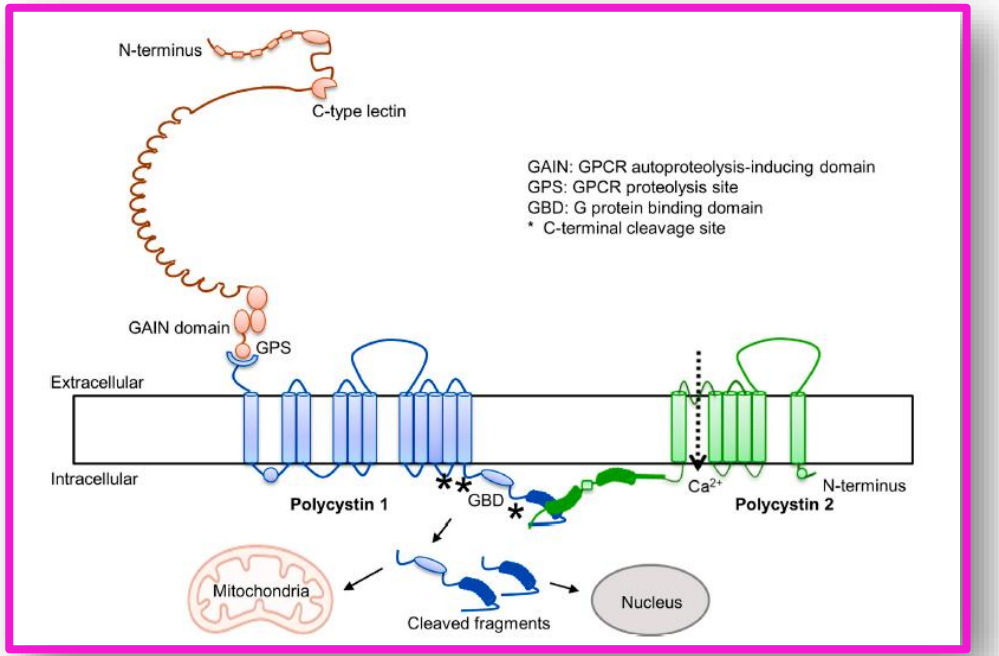
Επειδή αιτία της νόσου είναι οι **γενετικές παραλλαγές** (μεταλλάξεις) ή βλάβες **σε ένα μόνο γονίδιο** (**μονογονιδιακή** όχι πολυγονιδιακή)

PKD1, PKD2 (93%)

GANAB, IFT140, DNAJB11, ALG9, ALG8, ALG5, NEK8, NKHD1 (7%)

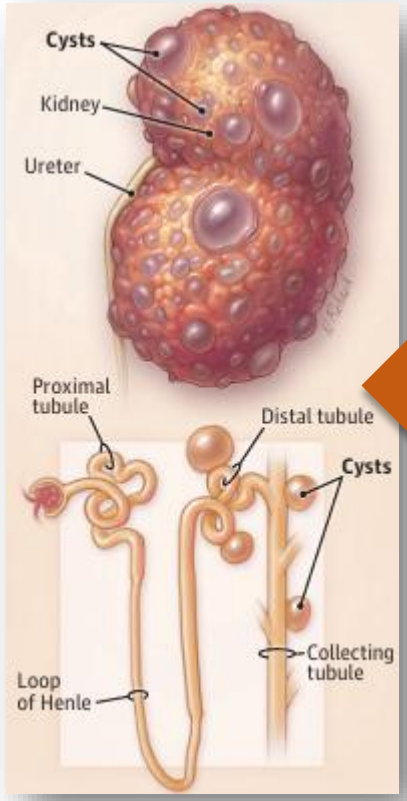


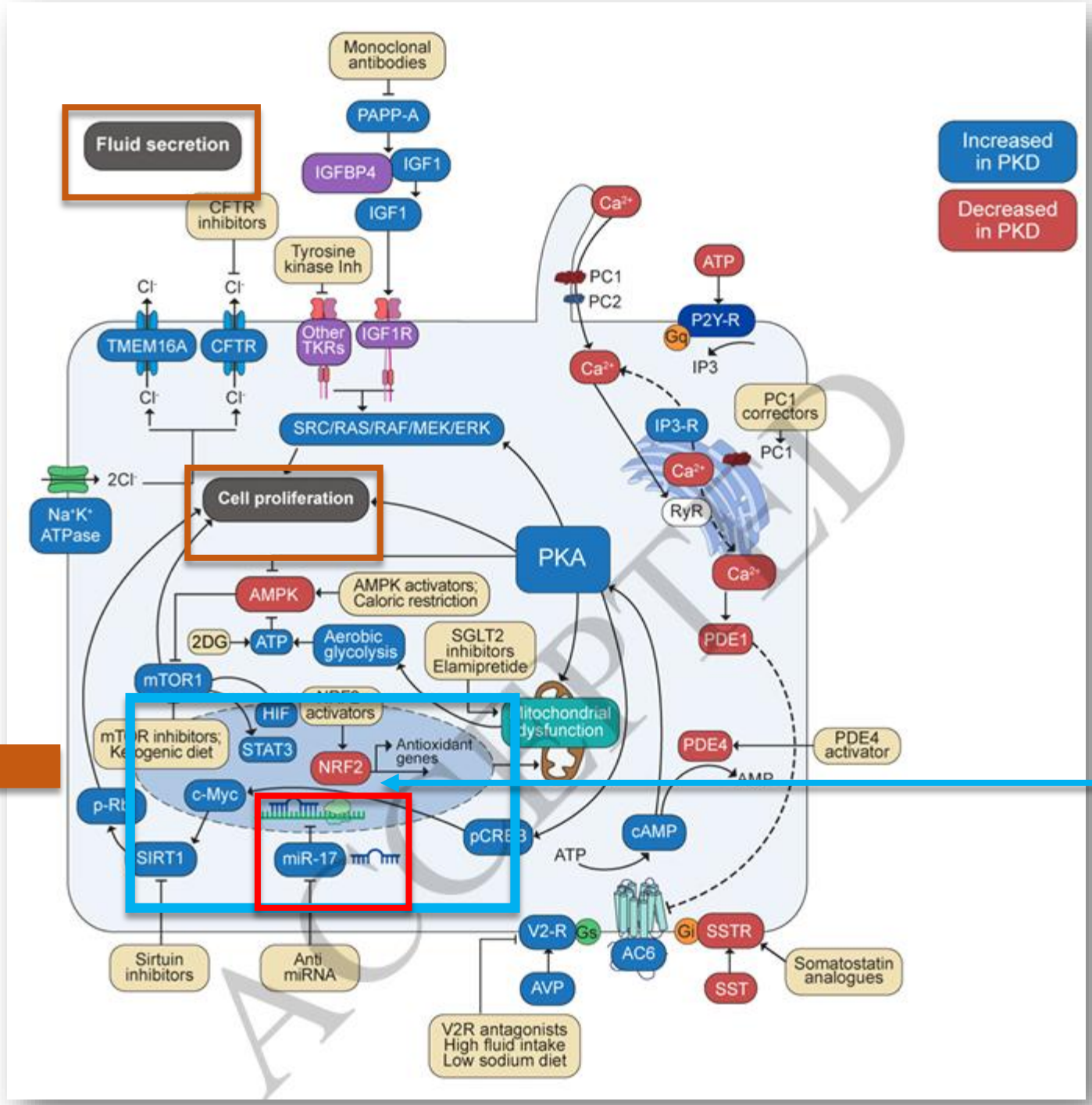
Διαταραχή της δομής και της λειτουργίας των Πολυκυστινών 1 και 2



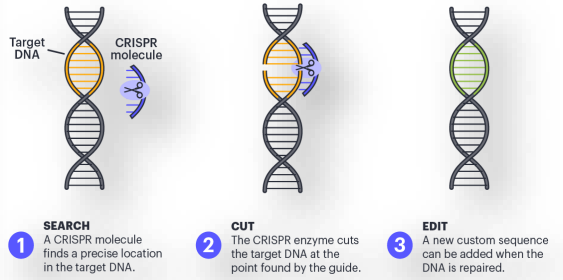
Άπω νεφρικό σωληναριακό κύτταρο

Watering Collecting Duct Cysts: Are **Aquaporin2 Progenitors** the Answer?

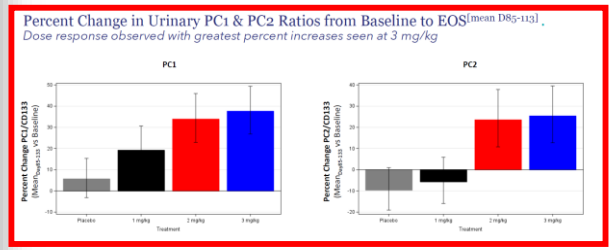




Επιβράδυνση πορείας νόσου (Tolvaptan, Metformin etc)



Οριστική θεραπεία (όχι καθολική)



Renal plasticity revealed through reversal of polycystic kidney disease in mice

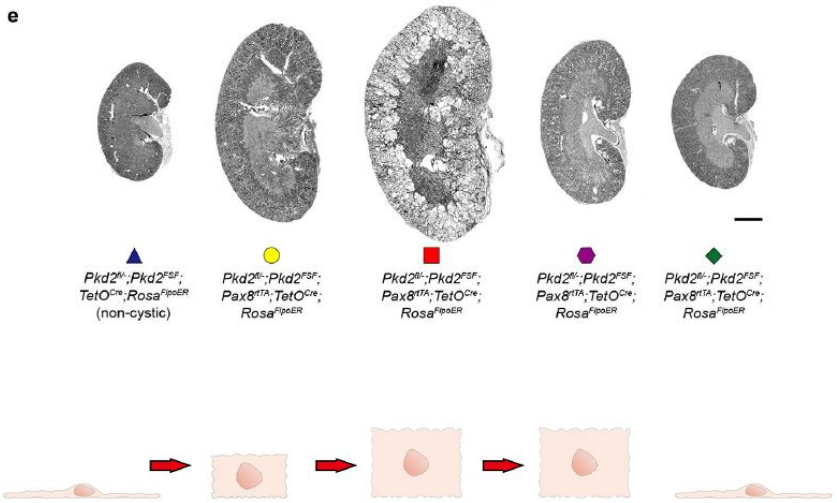
Ke Dong, Chao Zhang, Xin Tian, Daniel Coman, Fahmeed Hyder, Ming Ma & Stefan Somlo

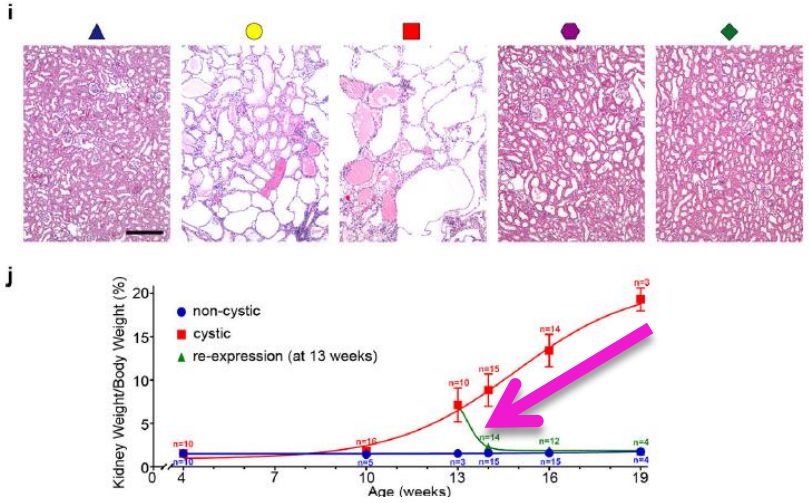
Nature Genetics **volume 53**, pages1649–1663 (2021)

Θα είναι **αποτελεσματική** μια γενετική θεραπεία της νόσου?

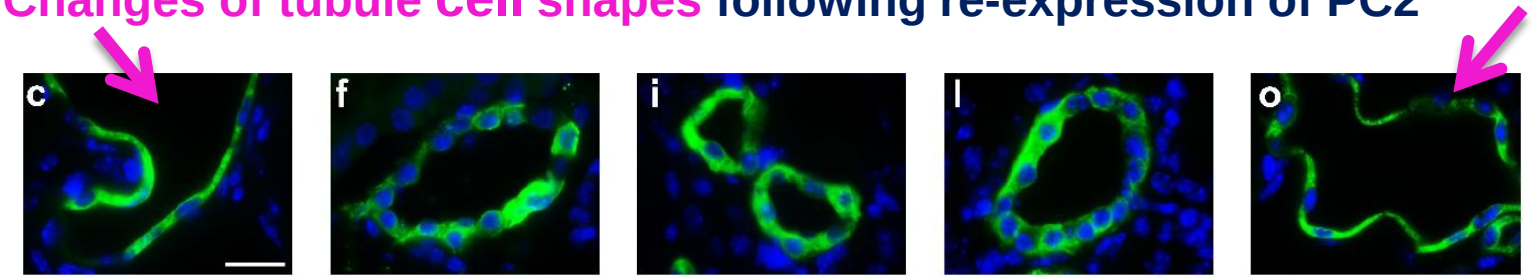
We constructed a mouse model in which adult **inactivation** **of either *Pkd* gene can be followed by reactivation of the gene at a later time**.

Using this model, we show that **re-expression** of *Pkd* genes in cystic kidneys results in **rapid reversal of ADPKD**

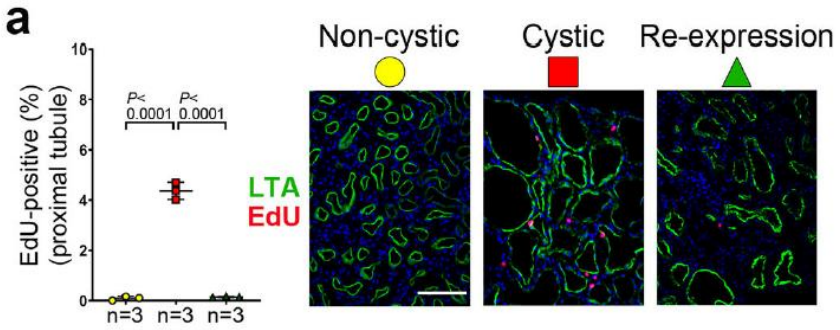




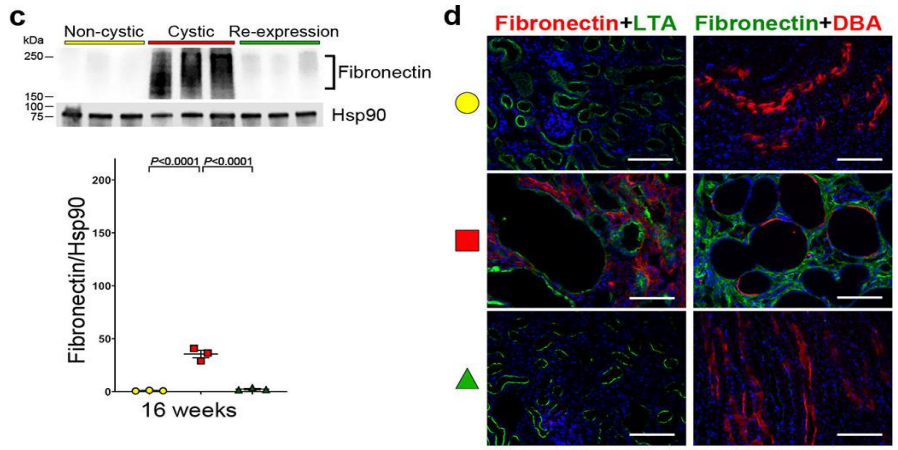
Changes of tubule cell shapes following re-expression of PC2



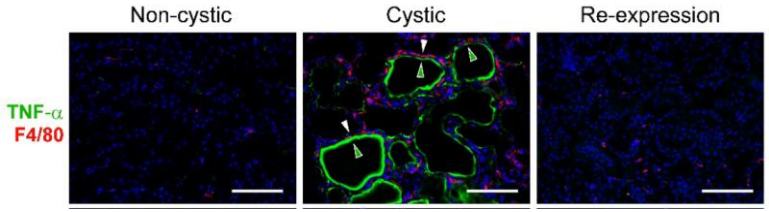
Decreased cyst cell proliferation following re-expression of PC2



Reversal of fibrotic changes in cystic kidneys following PC2-HA re-expression



Reversal of inflammatory changes in cystic kidneys following PC2-HA re-expresion



Renal plasticity revealed through reversal of polycystic kidney disease in mice Ke Dong, Chao Zhang, Xin Tian, Daniel Coman, Fahmeed Hyder, Ming Ma & Stefan Somlo *Nature Genetics* **volume 53**, pages1649–1663 (2021)

Ποιες γενετικές ιδιαιτερότητες υπάρχουν στην ΠΚΝ ?

Αυτοσωμιακή επικρατής:
ένα μόνο **μεταλλαγμένο γονίδιο** από τον **ένα γονέα** αρκεί για να προκαλέσει τη νόσο,
το άλλο αλληλόμορφο (αλλήλιο) από τον άλλο γονέα, **αναμένεται να είναι φυσιολογικό**

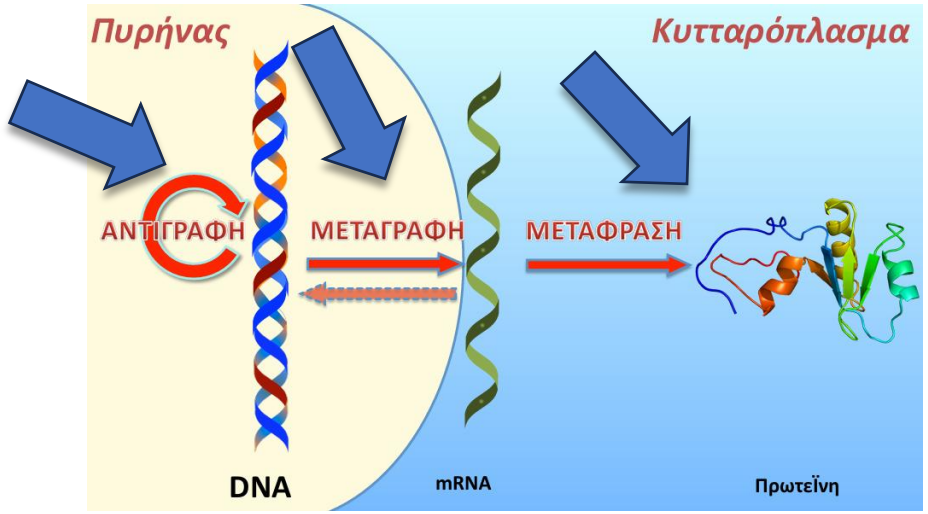
Η ADPKD κληρονομείται με τρόπο επικρατούντα αλλά **συμπεριφέρεται ως υπολειπόμενη βλάβη σε κυτταρικό επίπεδο [cellular recessive]**
Για να εκδηλωθεί χρειάζεται
Δεύτερο χτύπημα (**second hit**): **σωματική μετάλλαξη** του (μη-μεταλλαγμένου) αλληλίου του σωληναριακού επιθηλιακού κυττάρου. Κλωνική ανάπτυξη.
Μείωση της έκφρασης του PKD1 (ή PKD2) κάτω από ένα όριο: **δοσο-εξαρτώμενη έναρξη**
(↓ 20-30 % λειτουργικότητας PC-1 – PC-2) **[threshold model]** [κύρια μετάλλαξη + πιθανή σωματική μετάλλαξη + άλλοι παράγοντες που επηρεάζουν έκφραση και λειτουργικότητα πολυκυστινών]

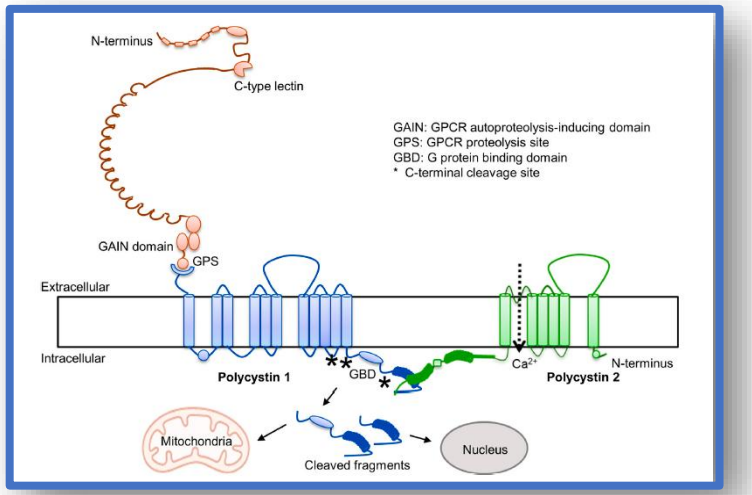
Genotype-Specific (Genotype-driven) (genetic testing)

Genotype-agnostic approaches "one-size-fits-all"

Σε ποιο σημείο των γενετικών δρόμων μπορούμε να παρέμβουμε και πως?

(έλεγχος ποιότητας διακίνηση πρωτεΐνης)





Micro-RNAs (mi-RNAs): non-coding μικρά RNAs που λειτουργούν ως **αναστολείς της έκφρασης του messenger RNA** (m-RNA)
[κατά τη πρωτεϊνική σύνθεση στα ριβοσωμάτια]

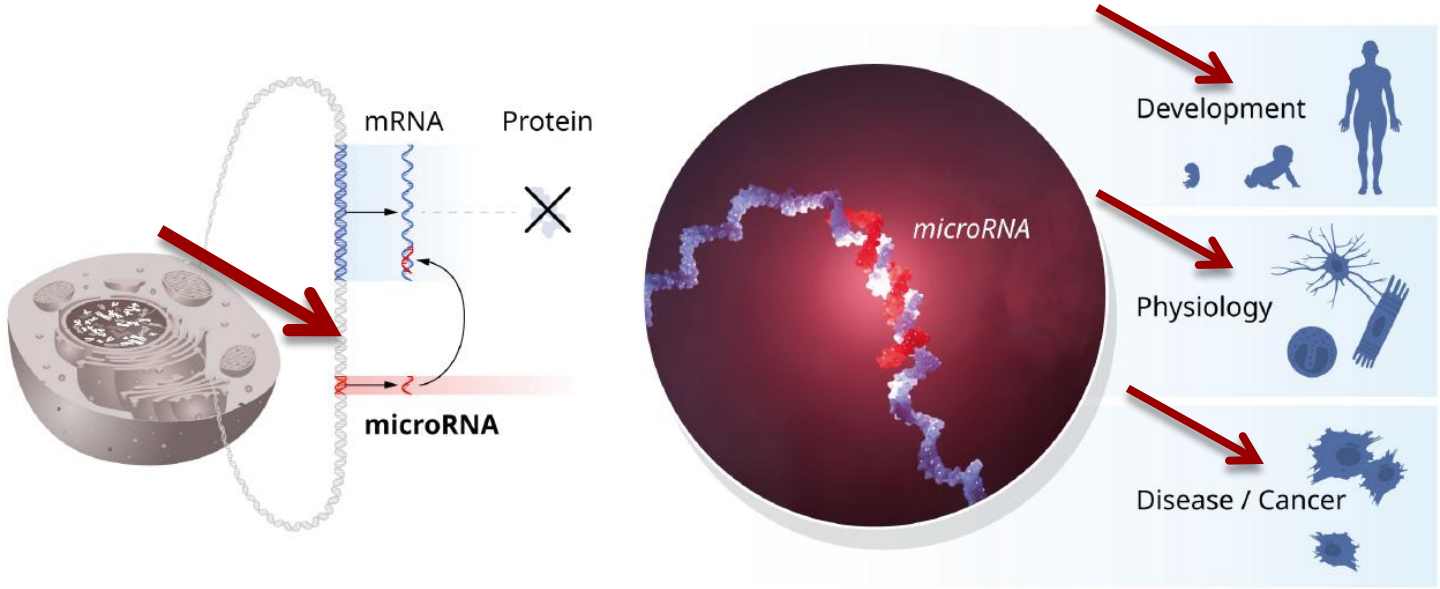
the 2024 Nobel Prize in Physiology or Medicine
jointly to
Victor Ambros and Gary Ruvk
for the discovery of microRNA and its role in post-transcriptional gene regulation

Tiny RNAs with profound physiological importance

DNA διπλής έλικας: δομή (hardware)
Micro-RNAs : ρύθμιση λειτουργίας (software)

Πως μπορούμε να παρέμβουμε?

Ανοίγουν ή κλείνουν τη στρόφιγγα παραγωγής των πρωτεϊνών μετά τη μεταγραφή
(καθορίζουν αν το messenger RNA που παράχθηκε θα οδηγήσει σε παραγωγή πρωτεϊνών ή όχι)

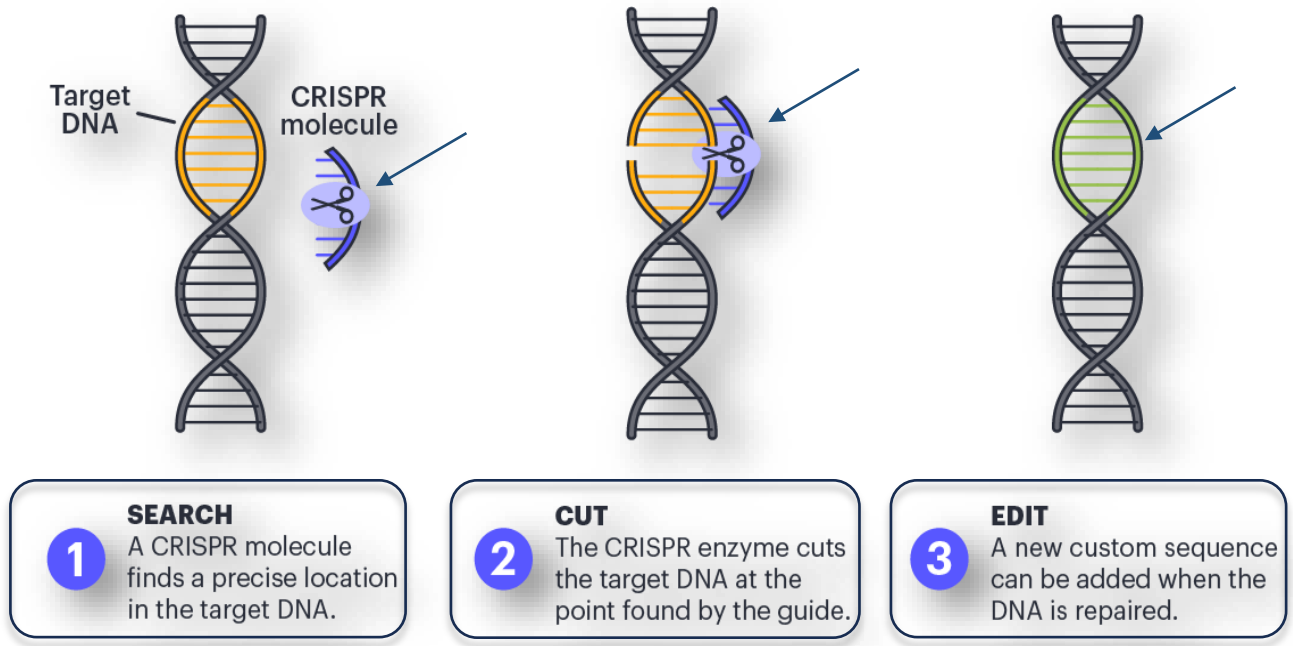


"The development of a method for genome editing"

Nobel Prize in Chemistry 2020 to
Emmanuelle Charpentier
Max Planck Unit for the Science of Pathogens, Berlin, Germany
Jennifer A. Doudna
University of California, Berkeley, USA

CRISPR/Cas9

Πως μπορούμε να παρέμβουμε?

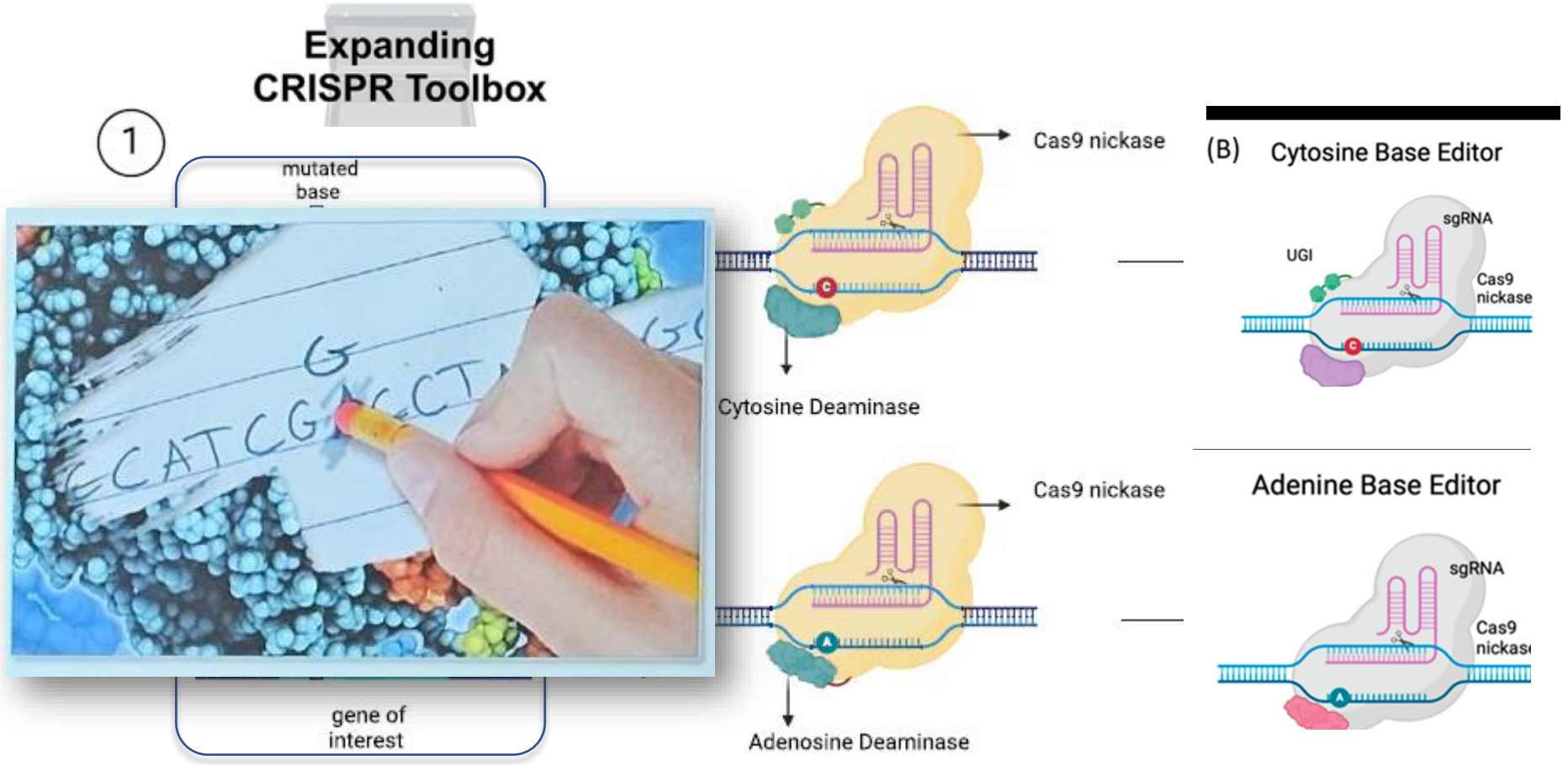


FDA NEWS RELEASE
FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease

FDA clears first CRISPR treatment for a second disease, beta thalassemia

Base editing: **nCas9 are fused to cytidine or adenosine deaminases** to induce **substitutions or base edits without inducing double-strand breaks (**reducing the risk of off-target effects**)**

Πως μπορούμε να παρέμβουμε?



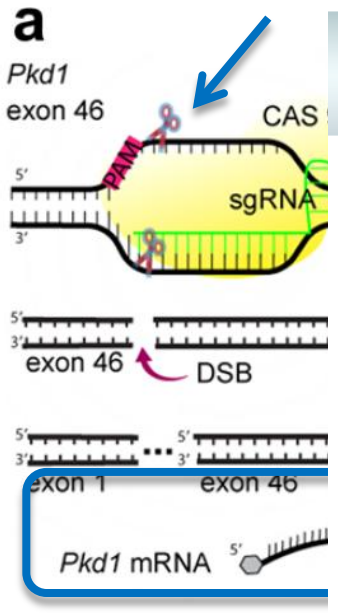
Cytosine Bes (CBE) can convert a **C:G to a T:A** base pair

Adenine Bes (ABEs) can convert A:T to G:C

Πως μπορούμε να παρέμβουμε?

Με συμπληρωματικά ολιγονουκεοτίδια (**antisense oligonucleotides (ssASOs)**) ή φάρμακα που **εξουδετερώνουν τα κωδικόνια πρόωρου τερματισμού** και **επιτρέπουν τη συνέχεια της μεταγραφής (readthrough therapies)**

Τα **Oligonucleotides εναλλαγής ματίσματος (Splice-Switching Oligonucleotides - SSOs)** είναι μικρά, συνθετικά μόρια νουκλεϊκών οξέων (συνήθως τροποποιημένα αντινοήματα ολιγονουκλεοτίδια - ASOs) που χρησιμοποιούνται για την **τροποποίηση της διαδικασίας ματίσματος του προ-mRNA**.



nature COMMUNICATIONS

ARTICLE

Received 7 Jun 2016 | Accepted 22 Dec 2016 | Published 16 Feb 2017

DOI: 10.1038/ncomms14395 OPEN

microRNA-17 family promotes polycystic kidney disease progression through modulation of mitochondrial metabolism

Sachin Hajarnis[1,*], Ronak Lakhia[1,*], Matanel Yheskel[1], Darren Williams[1], Mehran Sorourian[2], Xueqing Liu[2], Karam Aboudehen[3], Shanrong Zhang[4], Kara Kersjes[2], Ryan Galasso[2], Jian Li[2], Vivek Kaimal[2], Steven Lockton[2], Scott Davis[2], Andrea Flaten[1], Joshua A. Johnson[5], William L. Holland[5], Christine M. Kusminski[5], Philipp E. Scherer[5], Peter C. Harris[6], Marie Trudel[7], Darren P. Wallace[8], Peter Igarashi[3], Edmund C. Lee[2], John R. Androsavich[2] & Vishal Patel[1]

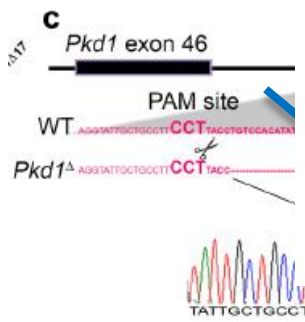
https://doi.org/10.1038/s41467-022-32543-2

cis-inhibition drives ase progression

Harini Ramalingam[1,4], Chun-Mien Chang[1], [1], Laurence Biggers[1], Andrea Flaten[1], Jesus Alvarez[1], rren P. Wallace[3], Edmund C. Lee[2] & Vishal Patel[1]

ιές αλλήλιο

Eliminating this m
stability, **raises Po**
cyst growth in cel
models.



nature COMMUNICATIONS

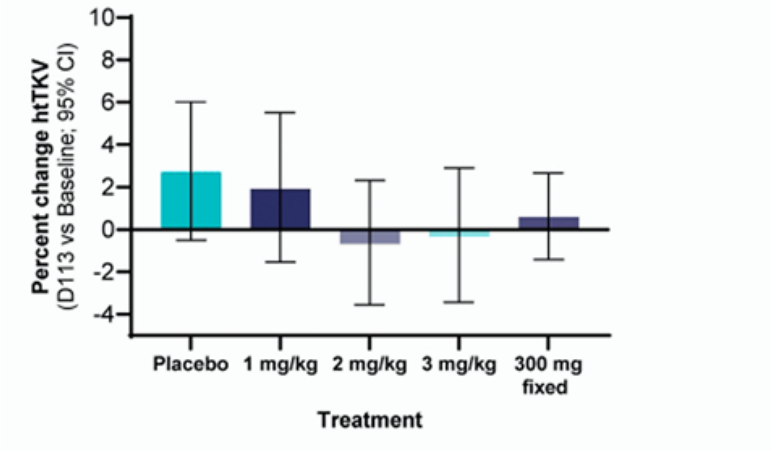
ARTICLE

https://doi.org/10.1038/s41467-019-11918-y OPEN

Discovery and preclinical evaluation of anti-miR-17 oligonucleotide RGLS4326 for the treatment of polycystic kidney disease

Edmund C. Lee[1], Tania Valencia[1], Charles Allerson[1], Annelie Schairer[1], Andrea Flaten[2], Matanel Yheskel[2], Kara Kersjes[1], Jian Li[1], Sole Gatto[1], Mandeep Takhar[1], Steven Lockton[1], Adam Pavlicek[1], Michael Kim[1], Tiffany Chu[1], Randy Soriano[1], Scott Davis[1], John R. Androsavich[1], Salma Sarwary[1], Tate Owen[1], Julia Kaplan[1], Kai Liu[1], Graham Jang[1], Steven Neben[1], Philip Bentley[1], Timothy Wright[1] & Vishal Patel[2]

Figure: Percentage change in htTKV from baseline to end of study



Cohort 4 (clinical study 1b) data highlights: **REGULUS**

- Increases in urinary **PC1 and PC2 levels (PC1 p=0.026; PC2 p=0.014).**
- Mean **htTKV growth rate over 4 months** was **0.05%** (SE -0.86% to +0.92%) while **placebo subjects** in the trial experienced a mean growth rate of **2.58%** (SE +1.09% to +4.10%).
- Farabursen at 300 mg demonstrated **a favorable safety and tolerability profile** in this study, consistent with earlier cohorts.

Novartis to acquire Regulus Therapeutics and farabursen, an investigational microRNA inhibitor to treat ADPKD, the most common genetic cause of renal failure

Apr 30, 2025 [$ 1.7 billion]

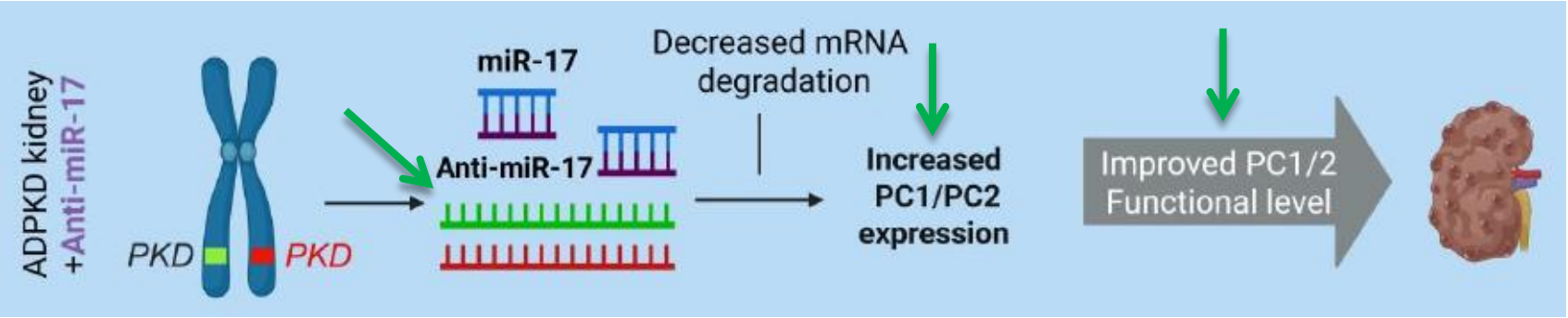
WCN26-7987

FARABURSEN INCREASES URINARY POLYCYSTIN 1 AND 2 AND REDUCES HEIGHT-ADJUSTED TOTAL KIDNEY VOLUME GROWTH IN PATIENTS WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

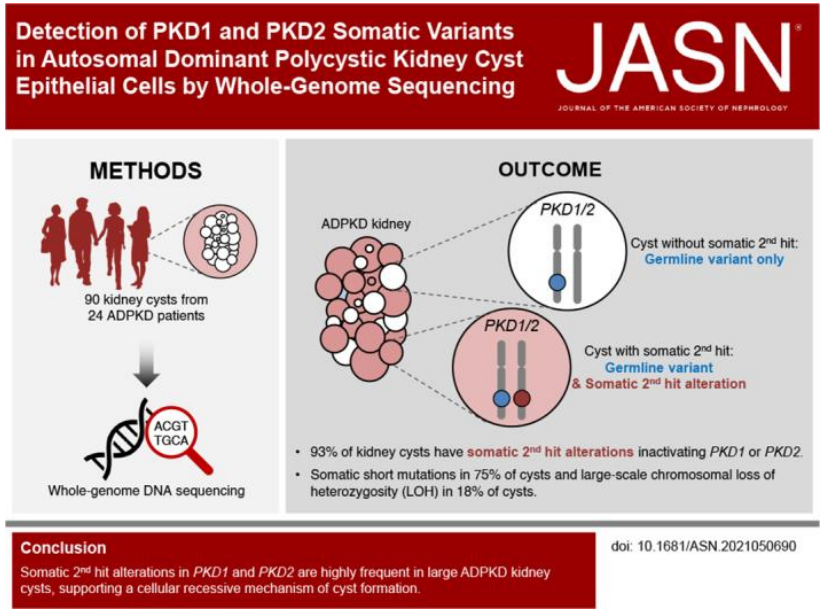
A meeting with U.S. Food and Drug Administration (FDA) and had confirmed alignment with the FDA …. including a **12-month htTKV endpoint planned** to support **Accelerated Approval** and a **24-month eGFR endpoint** to support **Full Approval**.

A single, pivotal Phase 3 study is planned to be initiated **in the third quarter of this year**.

"Genotype-agnostic approaches" εξαρτώνται κυρίως από την **ακεραιότητα του σωματικού αλληλόμορφου**



Emerging Therapies in Autosomal Dominant Polycystic Kidney Disease
Chen, Christopher Y.[1,a]; Hadla, Mohamad[2]; Khambati, Ibrahim[2]; Kashyap, Sonu[3]; Westerfield, Vanessa[1]; Fedeles, Sorin[4]; Besse, Whitney[5]; Hopp, Katharina[6]; Harris, Peter C.[7]; Patel, Vishal[8]; Chini, Eduardo[3]; Salih, Mahdi[9]; Barry, Michael A.[10]; Chebib, Fouad T.[2,a]
Kidney360 ():10.34067/KID.0000001109, December 12, 2025. | *DOI:* 10.34067/KID.0000001109



58% (14/24) of cysts had a detectable PKD1 somatic variant, with 5/6 participants having **at least one cyst** with a somatic variant.

Τι να περιμένουμε και πως θα χειριστούμε τα δεδομένα?

Εάν το farabursen (anti-miR-17) **αποδειχθεί αποτελεσματικό**

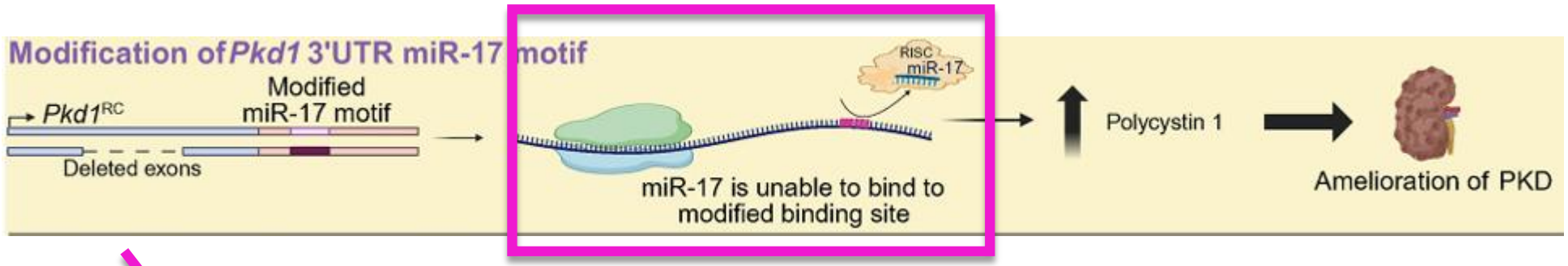
1. Είτε ένα **μεγάλο ποσοστό των κύστεων** έχουν *φυσιολογικό* σωματικό αλλήλιο
2. Είτε **το όφελος** για τη νεφρική λειτουργία οφείλεται στην **εξάλειψη** μόνον **ενός αριθμού κύστεων**
3. Είτε η αναστολή της δράσης του miR-17 έχει **και άλλα οφέλη** πέρα από την αύξηση της PC1.

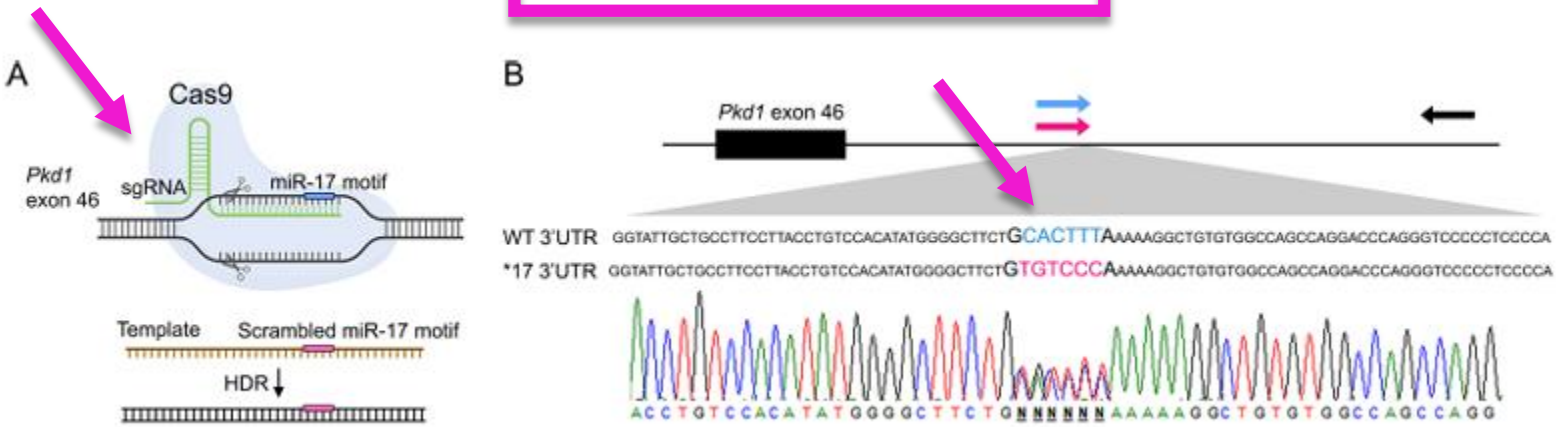
Emerging Therapies in Autosomal Dominant Polycystic Kidney Disease
Chen, Christopher Y.[1,a]; Hadla, Mohamad[2]; Khambati, Ibrahim[2]; Kashyap, Sonu[3]; Westerfield, Vanessa[1]; Fedeles, Sorin[4]; Besse, Whitney[5]; Hopp, Katharina[6]**; Harris, Peter C.[7]; Patel, Vishal[8]**; Chini, Eduardo[3]; Salih, Mahdi[9]; Barry, Michael A.[10]; Chebib, Fouad T.[2,a]
Kidney360 ():10.34067/KID.0000001109, December 12, 2025. | *DOI:* 10.34067/KID.0000001109

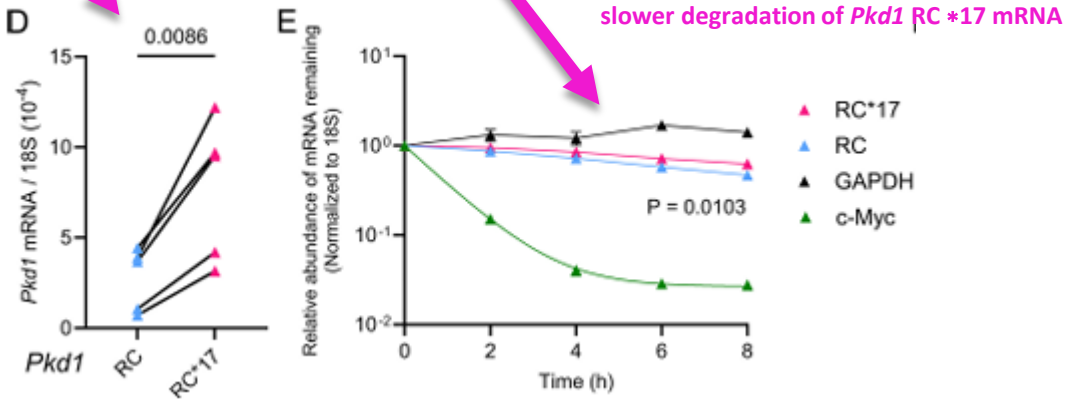
Είναι λογικό **να επηρεάσουν την αποτελεσματικότητα** της θεραπευτικής επέμβασης

- **Το ποσοστό** των σωματικών αλληλόμορφων που έχουν παρουσιάσει γενετικές παραλλαγές,
- **η χρονική στιγμή** που έγιναν (αν προηγήθηκαν ή όχι της γενετικής επεξεργασίας),
- αν σχετίζονται με **το μέγεθος της κάθε κύστης**,
- αν είναι **truncating ή non-truncating**

Substitution of six nucleotides within the miR-17 motif stabilizes Pkd1 mRNA.







slower degradation of *Pkd1* RC ∗17 mRNA

Nucleic Acids Research, 2026, **54**, gkaf1538
https://doi.org/10.1093/nar/gkaf1538
NAR Breakthrough Article

NAR Breakthrough Article

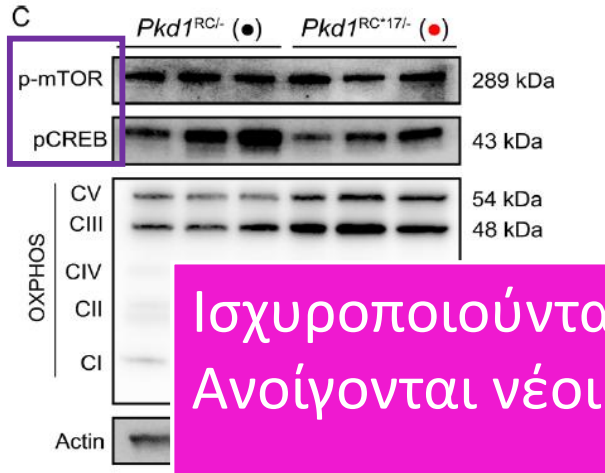
Disruption of a six-nucleotide miRNA motif improves *PKD1* dosage and ameliorates polycystic kidney disease

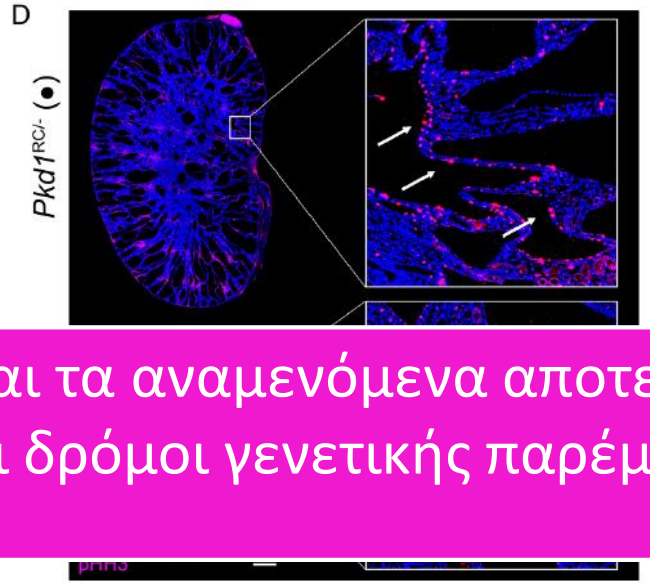
Ronak Lakhia*,†, Chunzi Song†, Laurence Biggers, Maggie Zumwalt, Jesus Alvarez, Arvind Somasundaram, Harini Ramalingam, Patricia Cobo-Stark, Vishal Patel

Department of Internal Medicine and Division of Nephrology, UT Southwestern Medical Center, Dallas, TX 75390, United States

*To whom correspondence should be addressed. Email: Ronak.lakhia@utsouthwestern.edu
†These authors contributed equally.

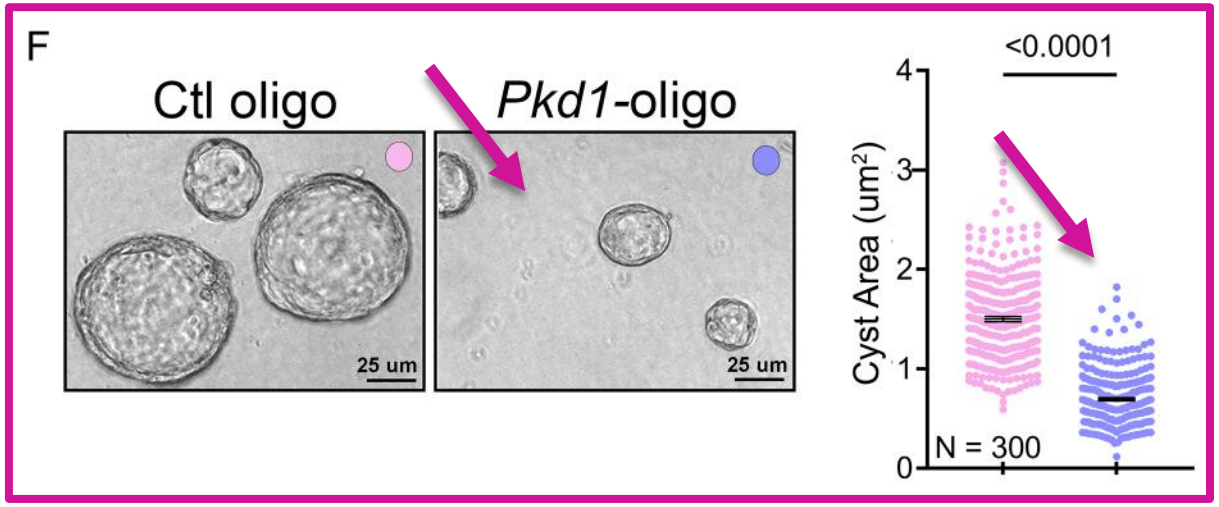
Mitochondrial dysfunction and hyperproliferation are reversed by PC1 restoration

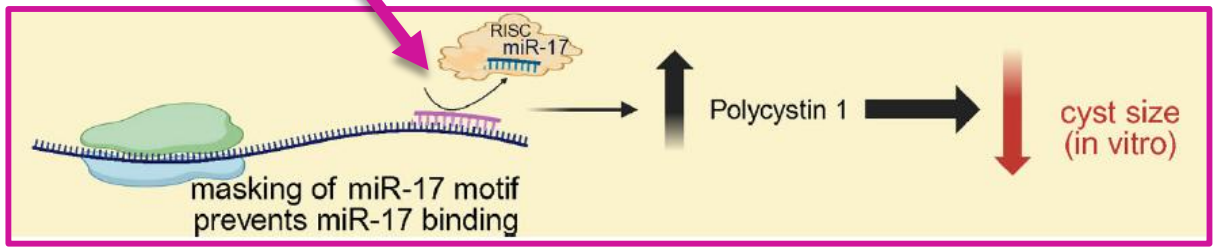




Pkd1-oligonucleotide increases PC1 expression and improves cyst parameters in mouse cellular PKD model

Ισχυροποιούνται τα αναμενόμενα αποτελέσματα από το Farabursen
Ανοίγονται νέοι δρόμοι γενετικής παρέμβασης-επεξεργασίας (με CRISPR/Cas9)





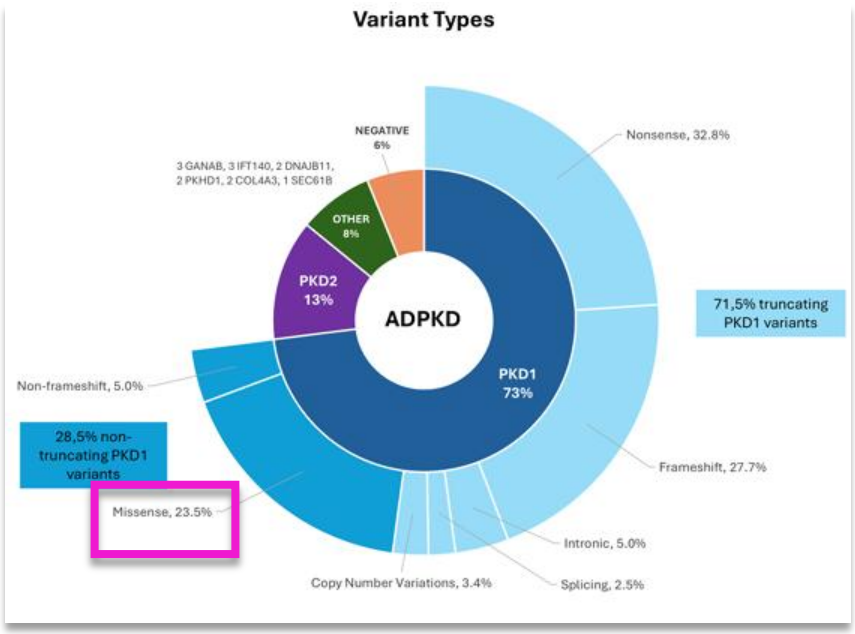
Genotype-Specific (Genotype-driven): τροποποίηση γενετικών παραλλαγών

Τύπος Γενετικής Παραλλαγής	Ορισμός	Αλλαγή νουκλεοτιδίου	Αλλαγή στο cDNA	Αλλαγή στην πρωτεΐνη
Synonymous *(Συνώνυμη)*	Αντικατάσταση ενός νουκλεοτιδίου, χωρίς να αλλάζει το αμινοξύ	ATG AGA (ref) c. 1 2 3 4 5 6 Met Arg p. 1 2 ↓ ATG AGG (var) Met **Arg**	c.6**A>G**	p.Arg2= or p.Arg2Arg
Missense *(Παρερμηνεύσιμη)*	Αντικατάσταση ενός νουκλεοτιδίου, αλλάζει το αμινοξύ	ATG AGA (ref) Met Arg ↓ ATG ATA (var) Met Ile	c.5**G>T**	p.Arg2Ile
Nonsense *(Ανερμηνεύσιμη)*	Αντικατάσταση ενός νουκλεοτιδίου, με δημιουργία κωδικόνιου τερματισμού	ATG AGA (ref) Met Arg ↓ ATG TGA (var) Met STOP	c.4**A>T**	p.Arg2**Ter** or p.Arg2**X**
Frameshift *(Πλαισιοτροποποιητική)*	Προσθήκη ή διαγραφή νουκλεοτιδίων (αριθμός όχι πολλαπλάσιος του 3)	ATG AGA CAG T Met Arg Gln ↓ ATG GAC AGT Met Asp Ser	c.4delA	p.Arg2fs
Non frameshift *(Εντός πλαισίου ανάγνωσης)*	Προσθήκη ή διαγραφή νουκλεοτιδίων (αριθμός 3 ή πολλαπλάσιος του 3)	ATG AGA CAG T Met Arg Gln ↓ ATG CAG Met Gln	c.4_6delAGA	p.Arg2del
Splice variant *(Παραλλαγή θέσης ματίσματος)*	Αντικατάσταση ενός νουκλεοτιδίου	AAGgtaatt... Lys intron ↓ AAGttaatt... Lys intron	c.21+1G>T	

Η κλινική χρήση του γενετικού ελέγχου στη νεφρολογία, ένας πρακτικός οδηγός

Τ. Πουλλή, Δ. Παλαιολόγου, Γ. Τσιρπανλής

Ελληνική Νεφρολογία 2025; 37 (3): 260 - 277



nature communications

Article

https://doi.org/10.1038/s41467-025-65997-1

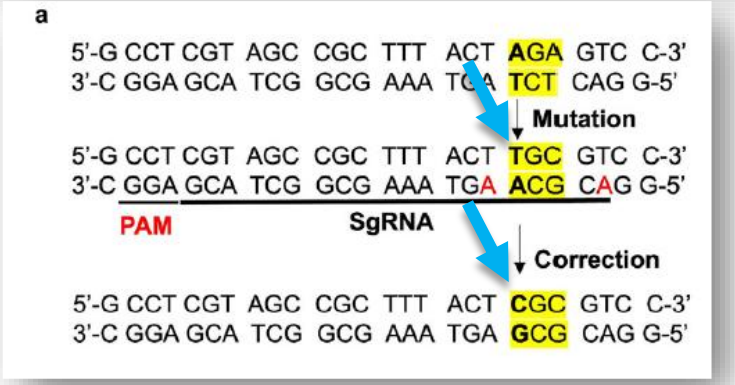
In vivo base editing rescues ADPKD in a humanized mouse model

Received: 23 January 2025

Accepted: 24 October 2025

Published online: 11 December 2025

Alice Shasha Cheng[1,2], Linda Xiaoyan Li[1,2], Julie Xia Zhou[1,2], Peter C. Harris[1,2], James P. Calvet[3] & Xiaogang Li[1,2]



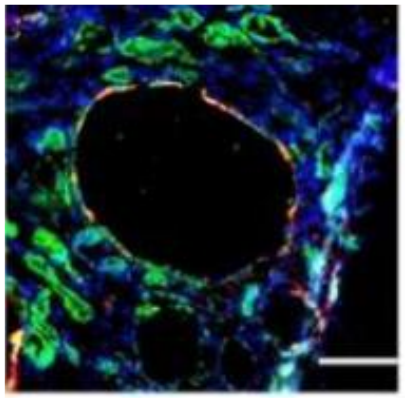
Adenine Bes (ABEs) convert A:T to G:C

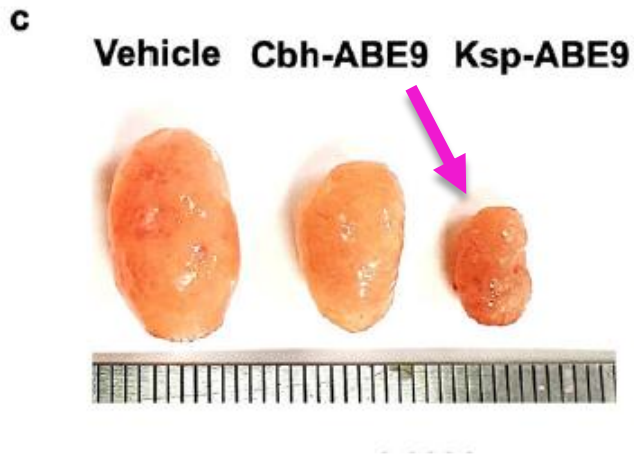
Genotype-Specific (Genotype-driven)

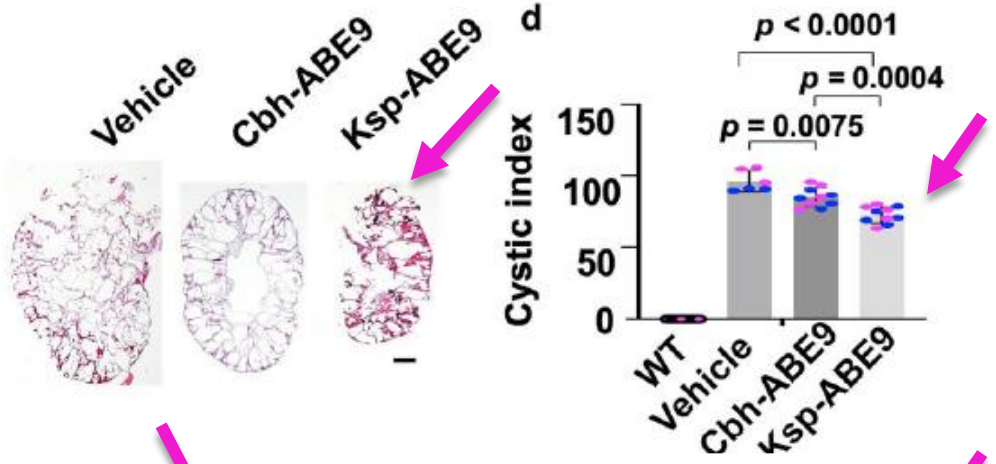
adeno-associated virus (AAV) delivered CRISPR-Cas9 gene editing [adenine base editor (ABE9)]

preventing disease in humanized Pkd1RC/RC mice carrying an arginine (R) to cystine (C) mutation that mimics a mutation in ADPKD patients

- **one dose** of the broadly expressed dual ABE9-AAV9 treatment **corrects the pathogenic variant in kidneys, hearts and livers**
- **one dose of the kidney specific promoter mediated dual-ABE9-AAV9 treatment corrects the Pkd1 gene mutation in the kidney base editor to target specific organs**

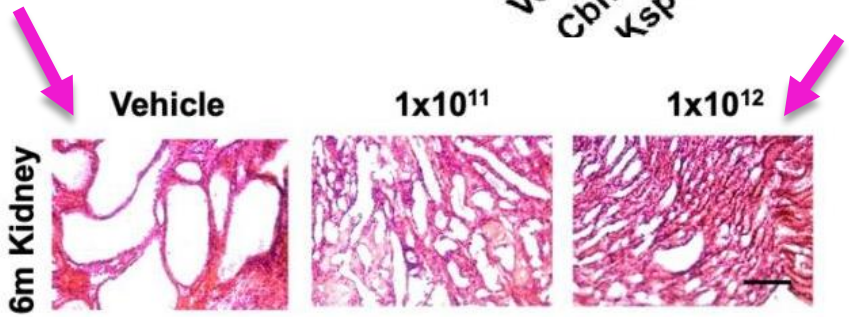




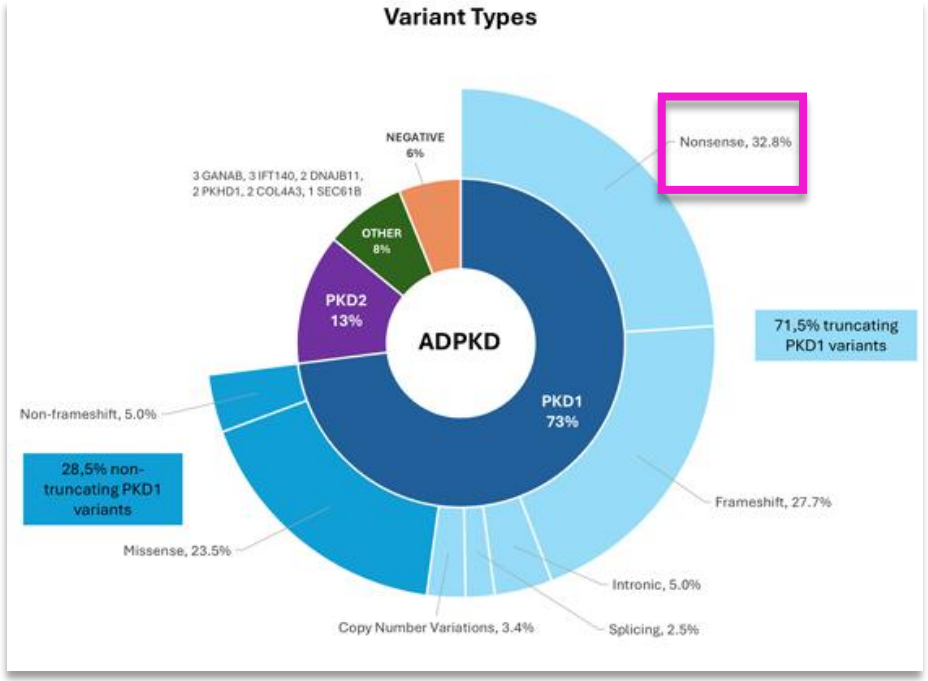


The average percentage of GFP-positive cells was about 19% among those cells in AAV9-Cbh-EGFP treated kidneys.

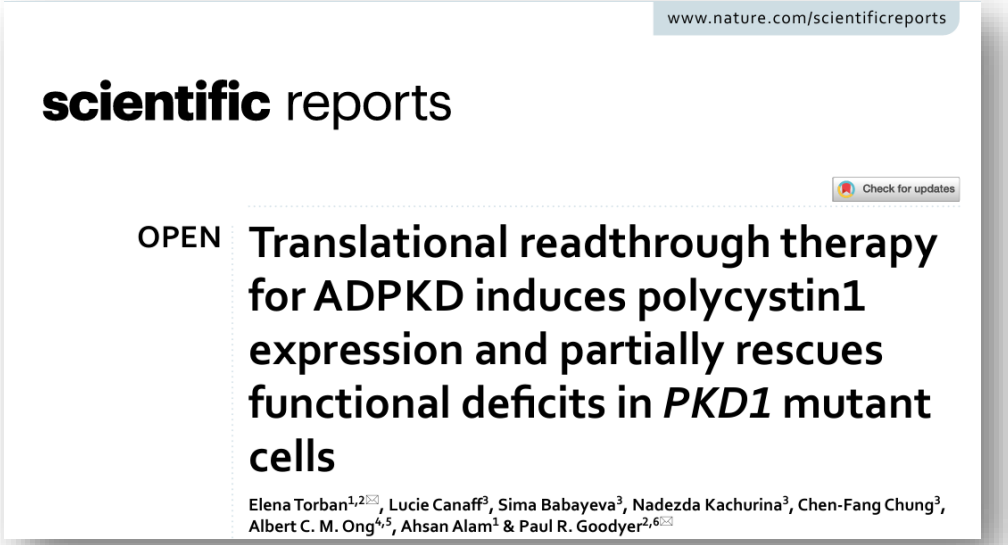
The average percentage of GFP positive cells was 27% among those cells in AAV9-Ksp-EGFP treated kidneys.



These preclinical studies support **a potential that single-dose genetic therapies may be through the correction of pathogenic variants to prevent ADPKD** development in the clinic

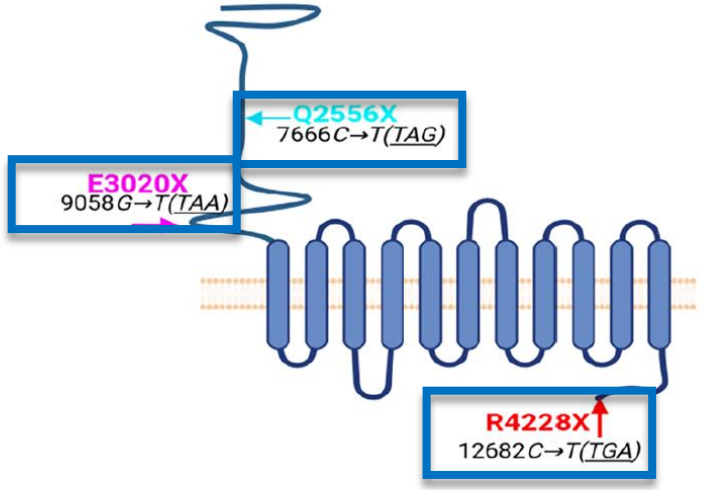


Genotype-Specific (Genotype-driven)



Translational readthrough: **Μεταφραστική παράκαμψη/ανάγνωση.**

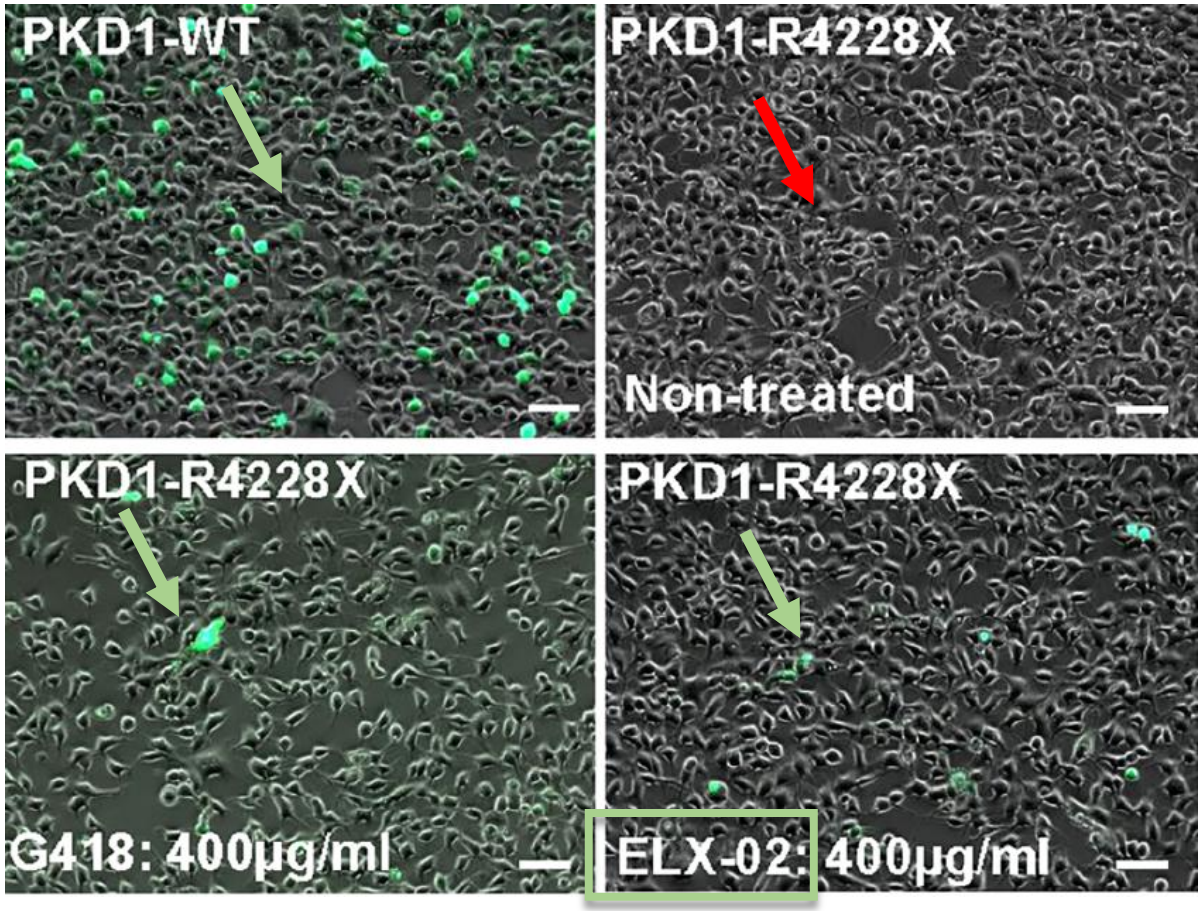
Stop codon readthrough: **Παράκαμψη του κωδικονίου λήξης.**

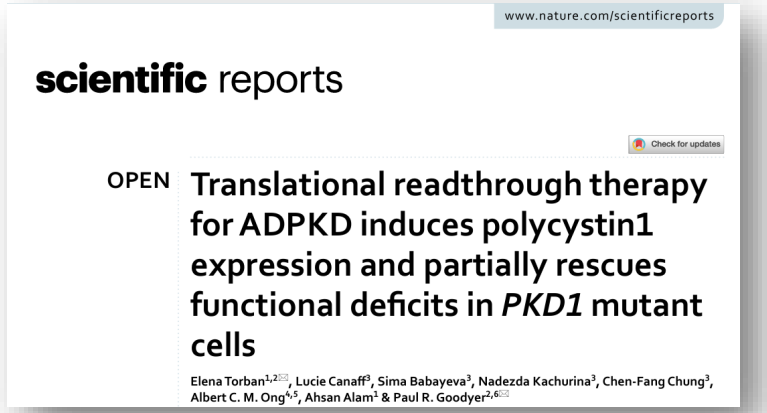


“Decoding Corruption”

“Sense from nonsense”

- G418 (Geneticin)
- Gentamicin
- Paromomycin.
- ELX-02 (NB124):to maximize readthrough while significantly reducing the nephrotoxicity and ototoxicity associated with traditional aminoglycosides.




www.nature.com/scientificreports

scientific reports

Check for updates

OPEN

Translational readthrough therapy for ADPKD induces polycystin1 expression and partially rescues functional deficits in *PKD1* mutant cells

Elena Torban[1,2], Lucie Canaff[3], Sima Babayeva[3], Nadezda Kachurina[3], Chen-Fang Chung[3], Albert C. M. Ong[4,5], Ahsan Alam[1] & Paul R. Goodyer[2,6]

We report that **aminoglycosides induce 8–25% expression of full-length Polycystin1 (PKD1 gene product)** and significantly **improve aberrant cell adhesion and cell signaling**. Based on our observations, we propose that aminoglycoside readthrough drugs show potential as therapeutic agents for ADPKD.

ADPKD: **δοσο-εξαρτώμενη έναρξη** (↓ 20-30 % λειτουργικότητας **PC-1** – PC-2) **[threshold model]**

Genotype-Specific (Genotype-driven)

Επέμβαση στο μηχανισμό συναρμογής (*splicing*) (ή **μάτισμα**)

[στάδιο επεξεργασίας του RNA κατά το οποίο απομακρύνονται τα ιντρόνια (ή εσώνια) συνενώνονται τα εξώνια και παράγεται το mRNA ώστε να αρχίσει η μεταγραφή].

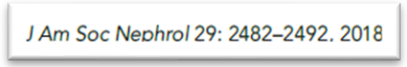
- σε **splicing (frame-shifted) αλλά και nonsense variants**
- **στην εγγενή διαταραχή του splicing** που οδηγεί σε πρώιμη διακοπή της μεταγραφής **στο γονίδιο PKD1** (μακρά περιοχή με πολυπυριμιδίνη στα εσώνια 21 και 22) και **επηρεάζει τα επίπεδα της Πολυκυστίνης-1**

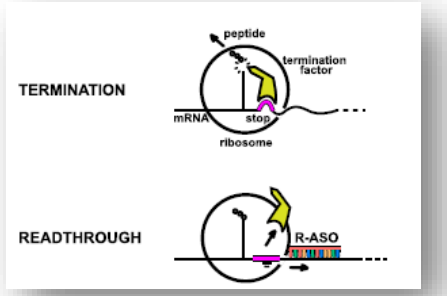

BASIC RESEARCH www.jasn.org

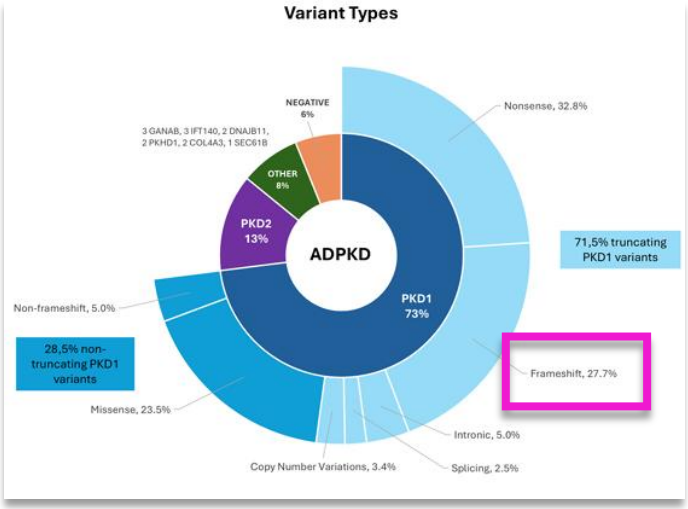
Human-Specific Abnormal Alternative Splicing of Wild-Type *PKD1* Induces Premature Termination of Polycystin-1

Wendy A. Lea,[1,2] Stephen C. Parnell,[1,3] Darren P. Wallace,[1,2,4] James P. Calvet,[1,3] Lesya V. Zelenchuk,[1,2] Nehemiah S. Alvarez,[5,6] and Christopher J. Ward[1,2,3]

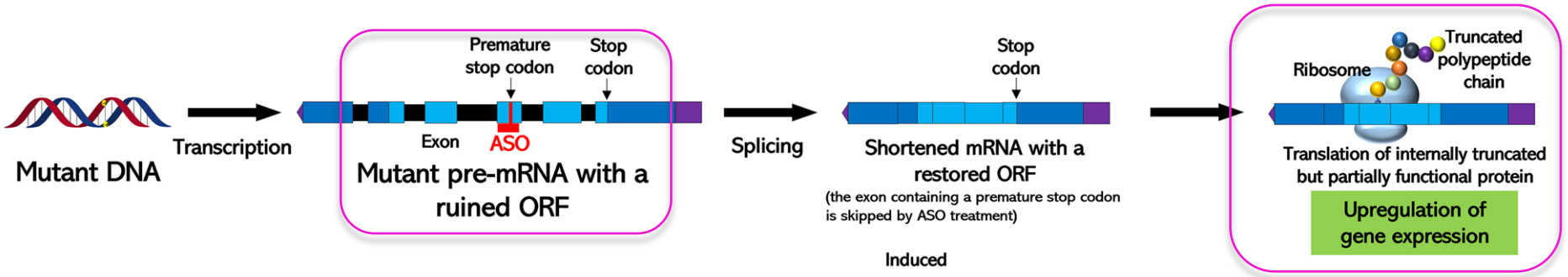
[1]The Jared Grantham Kidney Institute and Departments of [2]Internal Medicine, [3]Biochemistry and Molecular Biology, [4]Molecular and Integrative Physiology, and [5]Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, Kansas; and [6]De Novo Genomics, Kansas City, Kansas


J Am Soc Nephrol 29: 2482–2492. 2018





Με συμπληρωματικά ολιγονουκεοτίδια (**antisense oligonucleotides (ssASOs)**) που **εξουδετερώνουν τα κωδικόνια πρόωρου τερματισμού** και **επιτρέπουν τη συνέχεια της μεταγραφής (readthrough therapies)**



PYC-003 is an antisense oligonucleotide conjugated to a delivery peptide administered via intravenous infusion

PYC-003 antisense oligonucleotide (PMO) + PYC-003 peptide moiety = PYC-003 (PPMO)

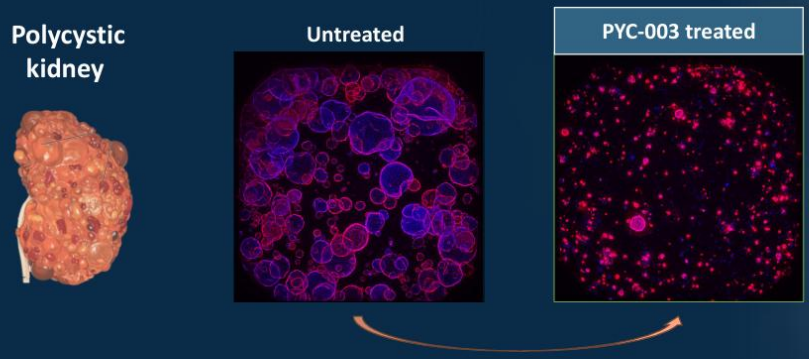
25 nucleotides
Binds to *PKD1* mRNA

30 amino acids
Facilitates delivery

Peptide-PMO conjugate
Administered intravenously

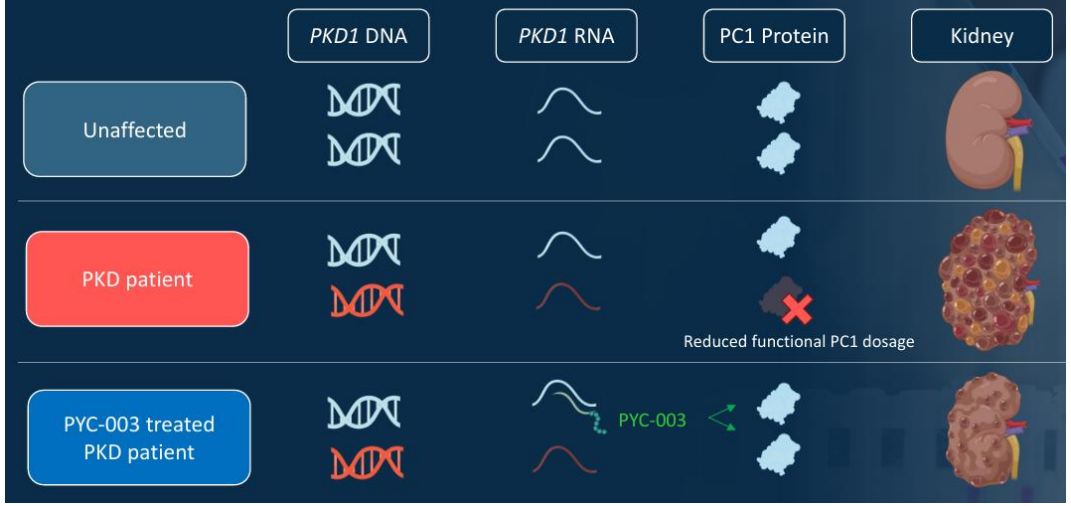
PMO = phosphorodiamidate morpholino oligomer

The modality is effective in 3D models at concentrations lower than what can safely be achieved *in vivo*



3D model derived from a patient with end-stage renal failure due to polycystic kidney disease treated with a single 60 µM dose of PPMO

PYC-003 is an RNA therapy with disease-modifying potential for ADPKD patients



The ongoing Phase 1a/1b studies are currently active across 5 sites with 2 more pending activation

Activation pending:

- Sunshine Hospital in collaboration with Doherty Clinical Trials
- Concord Hospital

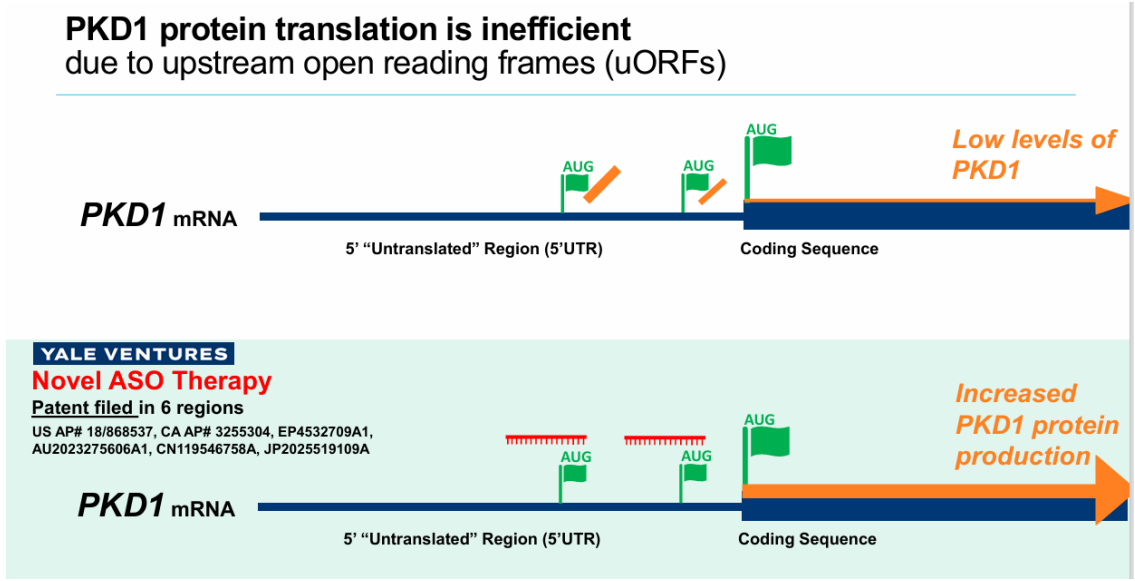
To learn more about this clinical trial visit clinicaltrials.gov, email pkd@pyctx.com or scan the QR code

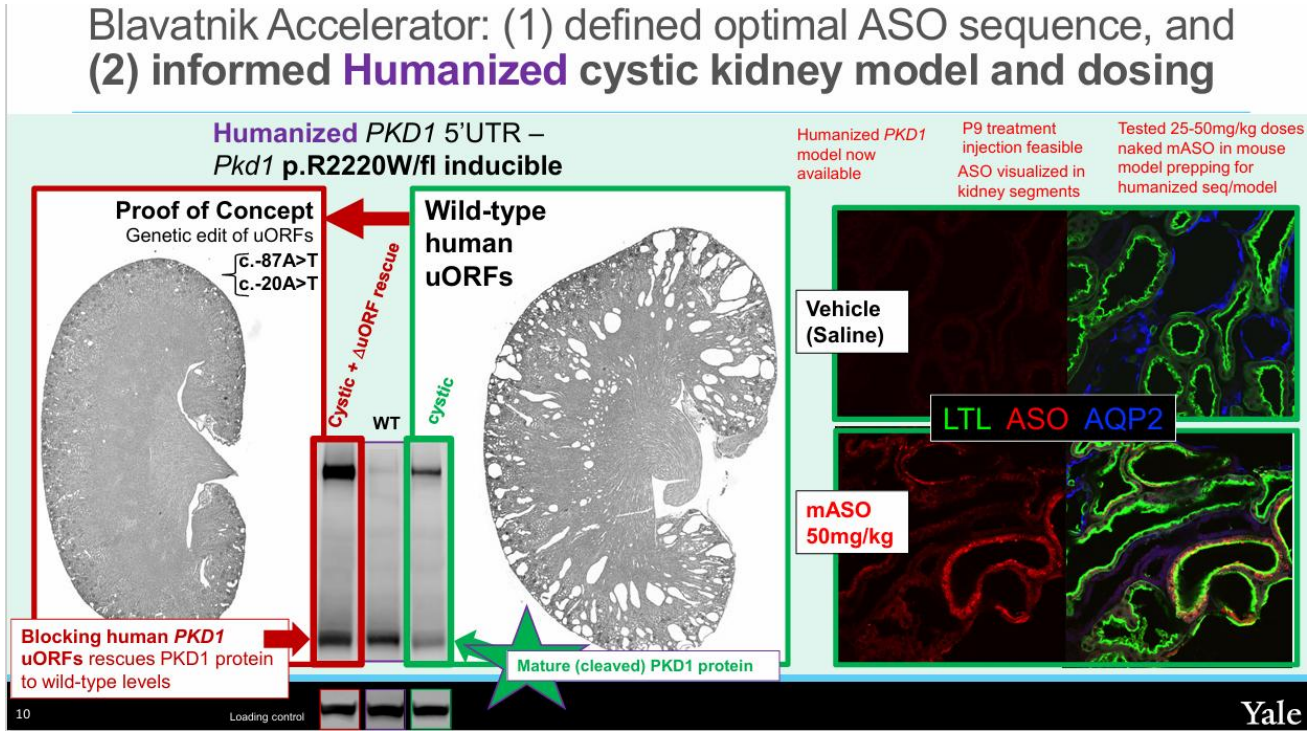
Antisense Oligonucleotide-Mediated Polycystin 1 Upregulation by Enhancing PKD1 Translation Has the Potential to Treat ADPKD

FR-OR054

Liang, Xuehai; Zhou, Hengbo; Zhang, Lingdi; Xu, Ye; Jain, Surendra K; Li, Jian; Thai, Rich Ming; Peng, Lansha; Yu, Xing-Xian (Scott); Wang, Yanfeng

Journal of the American Society of Nephrology 36(10S):10.1681/ASN.2025hpjwtmtc, October 2025. | *DOI:* 10.1681/ASN.2025hpjwtmtc

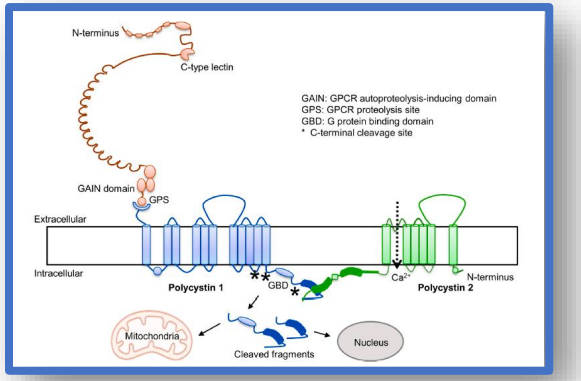




VX-407 is a first-in-class small-molecule corrector designed to treat Autosomal-Dominant Polycystic Kidney Disease (ADPKD) by correcting **defective folding** of the Polycystin-1 (PC1) protein.
By stabilizing these proteins, it targets the root cause of the disease to reduce cyst growth and slow kidney volume expansion in patients with specific *PKD1* gene variants.

Vertex

(έλεγχος ποιότητας διακίνηση πρωτεΐνης)



NCT07161037
/RecruitingPhase 2
A Phase 2a, Open-label, Single-arm Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of VX-407 in Subjects With Autosomal Dominant Polycystic Kidney Disease Who Have a Subset of PKD1 Gene Variants
The purpose of the study is to evaluate the effect of VX-407 on height-adjusted total kidney volume (htTKV), safety, tolerability, and pharmacokinetics (PK) of VX-407.

Gene-Based Therapeutic Strategies Under Development for ADPKD

Strategy	Vector footprint	Edit/cargo scope	Kidney deliverability (today)	Durability	Development status in ADPKD
CRISPRa (gene up-regulation)	Small	Mutation-agnostic (dosage)	Plausible with AAV/LNP	Potentially durable	Preclinical
Base editing	Medium (dual-AAV typical)	Point mutations (subset)	Feasible in organoids; in vivo delivery evolving	Durable	Preclinical (organoid correction)
Anti–miR-17 ASO	Small (single oligo)	Mutation-agnostic (dosage)	Favorable renal exposure	Redose	Clinical (Ph1b)
ERSGs / SSOs	Small	Nonsense or splicing variants	Feasible	Redose	Early clinical/ PoC

Emerging Therapies in Autosomal Dominant Polycystic Kidney Disease
Chen, Christopher Y.[1,a]; Hadla, Mohamad[2]; Khambati, Ibrahim[2]; Kashyap, Sonu[3]; Westerfield, Vanessa[1]; Fedeles, Sorin[4]; Besse, Whitney[5]; Hopp, Katharina[6]; **Harris, Peter C.[7]; Patel, Vishal[8];** Chini, Eduardo[3]; Salih, Mahdi[9]; Barry, Michael A.[10]; Chebib, Fouad T.[2,a]
Kidney360 ():10.34067/KID.0000001109, December 12, 2025. | *DOI:* 10.34067/KID.0000001109

Συνοψίζοντας

Οι ιδιαιτερότητες της πολυκυστικής νόσου των νεφρών (μονο-γονιδιακή με δοσο-εξαρτώμενη έναρξη) ευνοούν τη γενετική θεραπευτική

Παρεμβάσεις κατευθυνόμενες ή ανεξάρτητες από το γονότυπο του κάθε ασθενούς βρίσκονται σε εξέλιξη σε πειραματικά μοντέλα και σε κλινικές μελέτες

Η προοπτική ριζικής θεραπείας της πιο συχνής γενετικής νόσου των νεφρών δεν φαίνεται να είναι μακριά αλλά

η αποτελεσματικότητα της δεν αναμένεται καθολική,

θα εξαρτηθεί από συγκεκριμένους παράγοντες,
σχετιζόμενους ή όχι με τον γονότυπο ενώ

η μακροχρόνια ασφάλεια της μέλλει να αποδειχθεί.

Hope for diabetes: CRISPR-edited cells pump out insulin in a person — and evade immune detection

Edits create cells that don't trigger an immune response, allowing implant recipient to forego immune-suppressing drugs.

•Survival of Transplanted Allogeneic Beta Cells with No Immunosuppression

Authors: Per-Ola Carlsson, M.D., Ph.D., Xiaomeng Hu, Ph.D., Hanne Scholz, Ph.D., Sofie Ingvast, B.Sc., Torbjörn Lundgren, M.D., Ph.D., Tim Scholz, M.D., Ph.D., Olof Eriksson, Ph.D., Per Liss, M.D., Ph.D., Di Yu, Ph.D., Tobias Deuse, M.D., Olle Korsgren, M.D., Ph.D. https://orcid.org/0000-0002-8524-9547, and Sonja Schrepfer, M.D., Ph.D.Author Info & Affiliations

Published August 4, 2025

N Engl J Med 2025;393:887-894

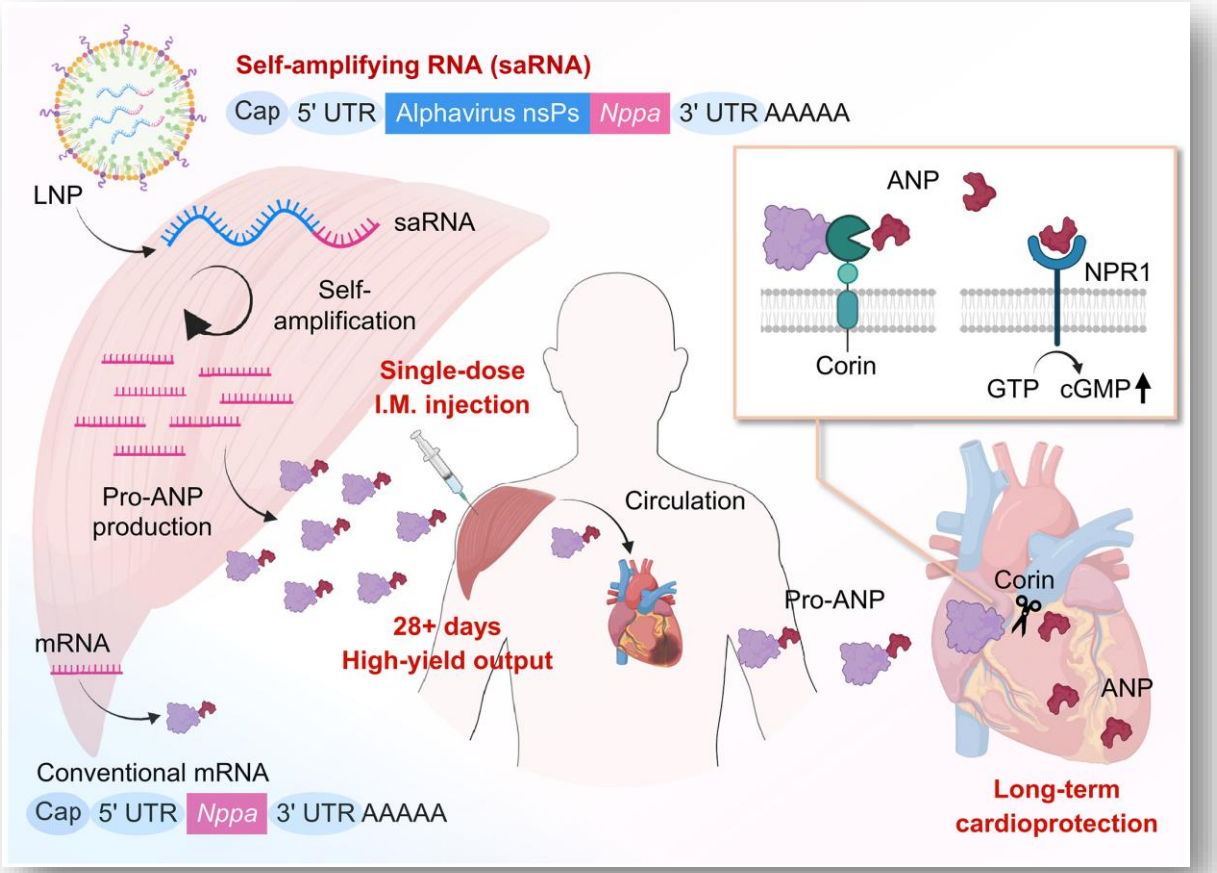
Single intramuscular injection of self-amplifying RNA of *Nppa* to treat myocardial infarction

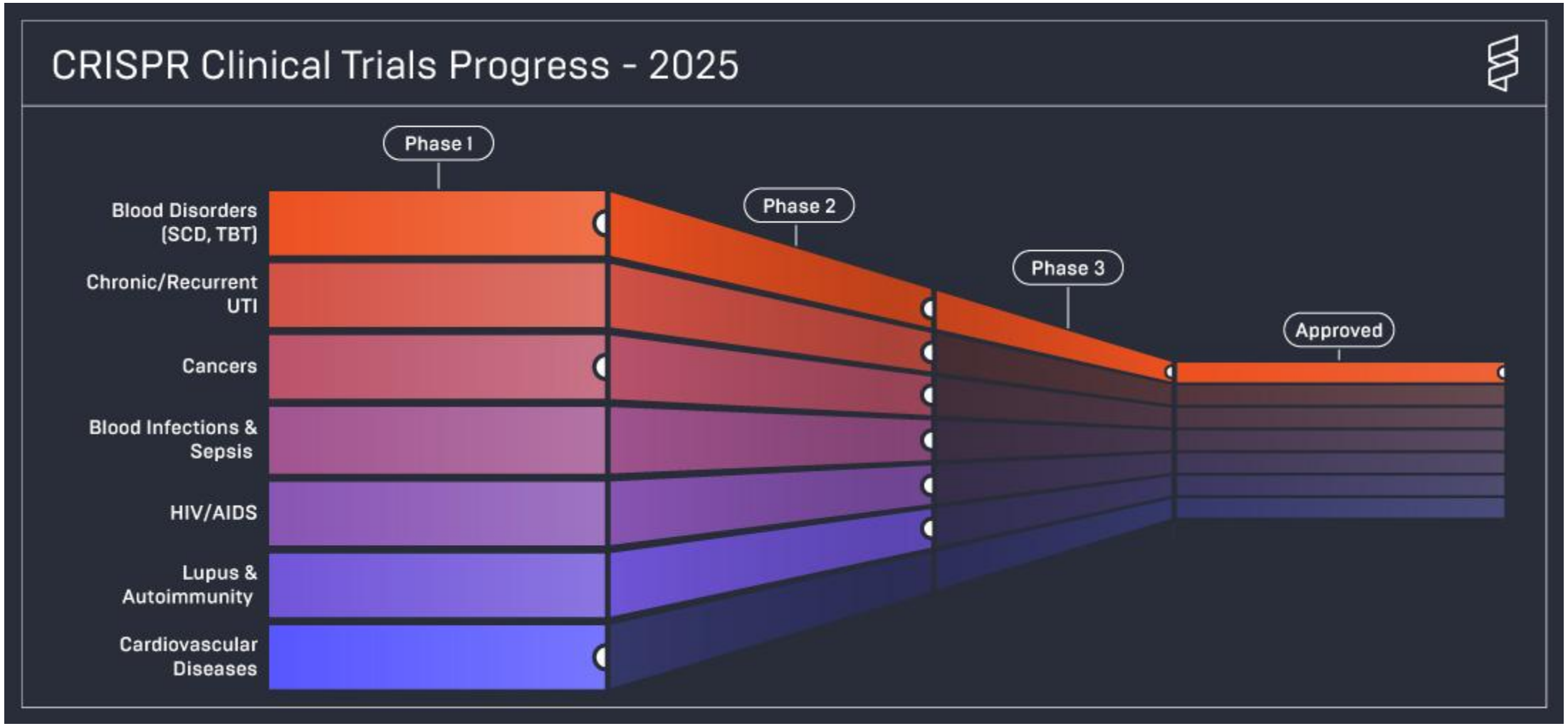
KAIYUE ZHANG

SCIENCE

5 Mar 2026

Vol 391, Issue 6789




CRISPR Clinical Trials Progress - 2025
Phase 1
Phase 2
Phase 3
Approved
Blood Disorders (SCD, TBT)
Chronic/Recurrent UTI
Cancers
Blood Infections & Sepsis
HIV/AIDS
Lupus & Autoimmunity
Cardiovascular Diseases

I would like to sincerely thank you for your support and timely collaboration during the feasibility assessment for the **CCYX082A12301 study in ADPKD**

Following the final global allocation, we were informed that **Greece was unfortunately not selected to participate in this study**. This decision was primarily driven by high global competition, with many countries demonstrating very strong interest and competitive recruitment rate.

Hub	Country
Americas	Argentina
Americas	Brazil
Americas	Canada
Americas	Colombia
Americas	Mexico
Americas	US
Asia	China
Asia	India
Asia	Japan
Asia	Korea
Asia	Taiwan
Asia	Thailand
Asia	Vietnam
EMEA	Denmark
EMEA	France
EMEA	Germany
EMEA	Italy
EMEA	Netherlands
EMEA	Portugal
EMEA	Spain
EMEA	Switzerland
EMEA	Turkey

Genetic testing Genetic testing should be offered systematically to people with ADPKD as applicable and **more education on the research and treatment benefits should be provided**. This is especially important as next-generation therapeutics target specific genotypes. **Information needs to be detailed and provided closer to the time of diagnosis. Making informed decisions earlier in their treatment could lead to better quality of life.**

KDOQI US Commentary on the KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

AJKD Vol 87 | Iss 4 | April 2026

Το μεγάλο μέγεθος του *PKD1 cDNA (~14 kB) είναι σοβαρός αρνητικός παράγοντας για μια «συμβατική» γονιδιακή θεραπεία*
"poor kidney delivery"

nature communications

Article

https://doi.org/10.1038/s41467-023-37449-1

The C-terminal tail of polycystin-1 suppresses cystic disease in a mitochondrial enzyme-dependent fashion

Received: 9 May 2022

Accepted: 17 March 2023

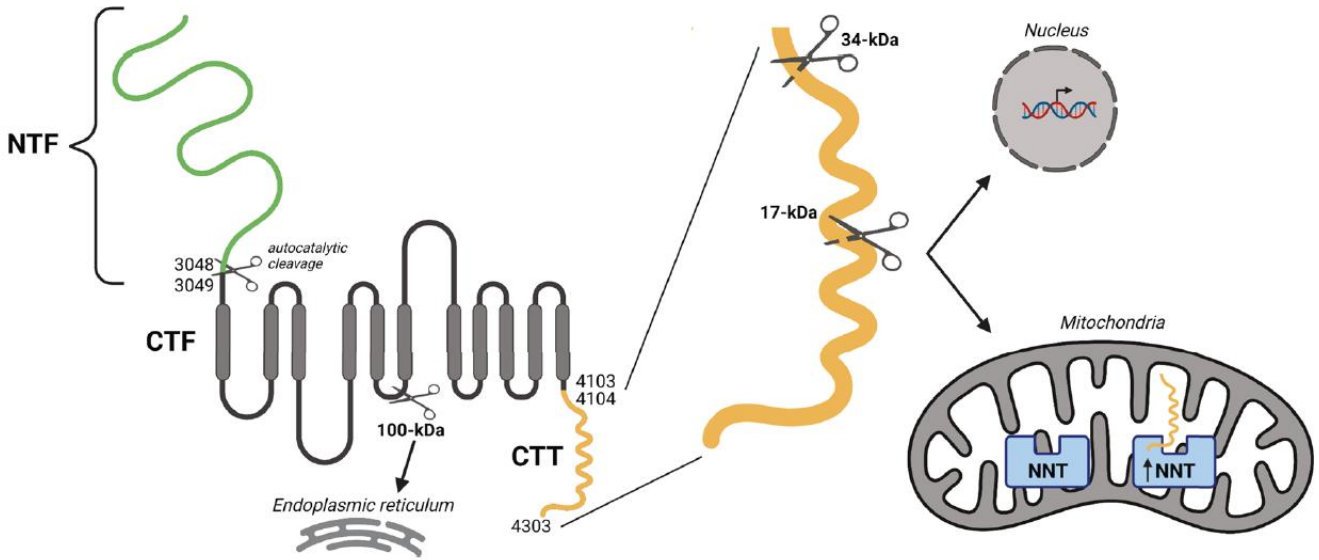
Published online: 30 March 2023

Laura Onuchic[1], Valeria Padovano[1], Giorgia Schena[1], Vanathy Rajendran[1], Ke Dong[2], Xiaojian Shi[1,3], Raj Pandya[1], Victoria Rai[1], Nikolay P. Gresko[1], Omair Ahmed[1], TuKiet T. Lam[4,5], Weiwei Wang[5], Hongying Shen[1,3], Stefan Somlo[2] & Michael J. Caplan[1]

Polycystin-1 C-terminal tail suppresses cystic phenotype in autosomal dominant polycystic kidney disease in a Pkd genotype-independent manner

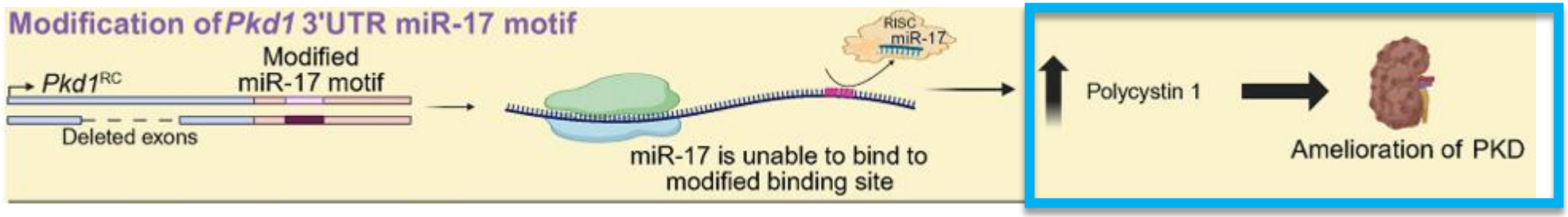
Authors: Victoria Rai victoria.rai@yale.edu, Laura Onuchic, and Michael Caplan

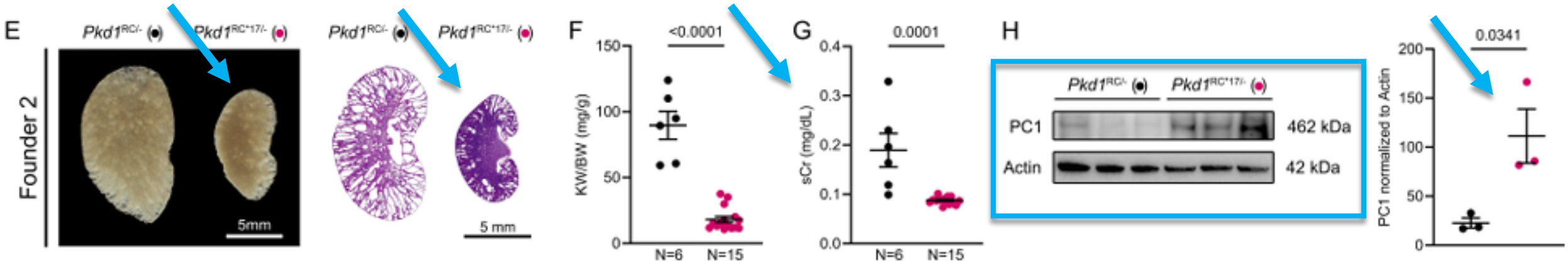
Publication: Physiology
Volume 41, Issue S1 2026



We report the unexpected finding that **expressing the C-terminal 200 aa** (CTT) of PC1 in an orthologous murine model of ADPKD **is sufficient to suppress the development of the cystic phenotype**.

Substitution of six nucleotides within the miR-17 motif ameliorates PKD





Nucleic Acids Research, 2026, **54**, gkaf1538
https://doi.org/10.1093/nar/gkaf1538
NAR Breakthrough Article

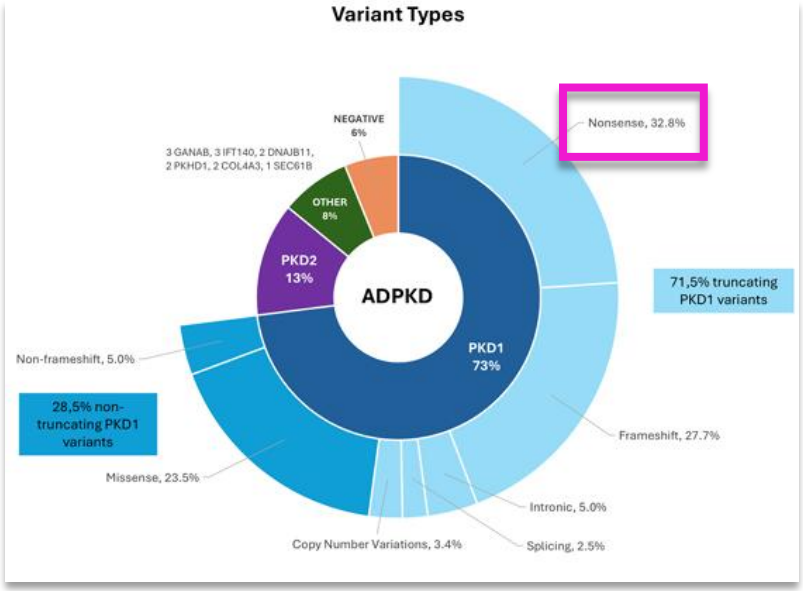
NAR Breakthrough Article OXFORD

Disruption of a six-nucleotide miRNA motif improves *PKD1* dosage and ameliorates polycystic kidney disease

Ronak Lakhia*,†, Chunzi Song†, Laurence Biggers, Maggie Zumwalt, Jesus Alvarez, Arvind Somasundaram, Harini Ramalingam, Patricia Cobo-Stark, Vishal Patel

Department of Internal Medicine and Division of Nephrology, UT Southwestern Medical Center, Dallas, TX 75390, United States

*To whom correspondence should be addressed. Email: Ronak.lakhia@utsouthwestern.edu
†These authors contributed equally.



www.nature.com/scientificreports

scientific reports

Check for updates

OPEN

Translational readthrough therapy for ADPKD induces polycystin1 expression and partially rescues functional deficits in *PKD1* mutant cells

Elena Torban[1,2]✉, Lucie Canaff[3], Sima Babayeva[3], Nadezda Kachurina[3], Chen-Fang Chung[3], Albert C. M. Ong[4,5], Ahsan Alam[1] & Paul R. Goodyer[2,6]✉

Translational readthrough: **Μεταφραστική παράκαμψη/ανάγνωση.**

Stop codon readthrough: **Παράκαμψη του κωδικονίου λήξης.**

Genotype-Specific (Genotype-driven)

Translational Readthrough-Inducing Drugs (TRIDs)
by binding to eukaryotic **ribosomes**, allowing them to **bypass Premature Termination Codons (PTCs) in mRNA.**
This **restores production of full-length**, functional proteins, offering a therapeutic approach **for genetic disorders caused by nonsense mutations**, such as **cystic fibrosis**, Duchenne muscular dystrophy, and recessive skin diseases.

“Decoding Corruption” **“Sense from nonsense”**

Farabursen (RGLS8429)

…και χωρίς παρενέργειες η γενετική παρέμβαση?

nature communications

Article

https://doi.org/10.1038/s41467-025-65799-5

The nucleobase guanine at the 3′-terminus of oligonucleotide RGLS4326 drives off-target AMPAR inhibition and CNS toxicity

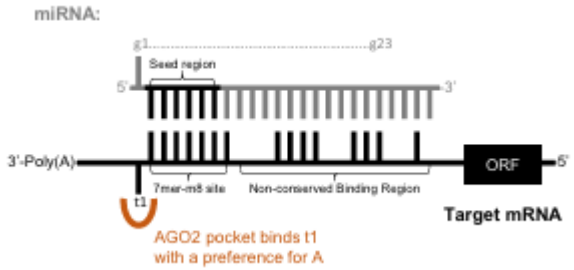
Received: 30 October 2024

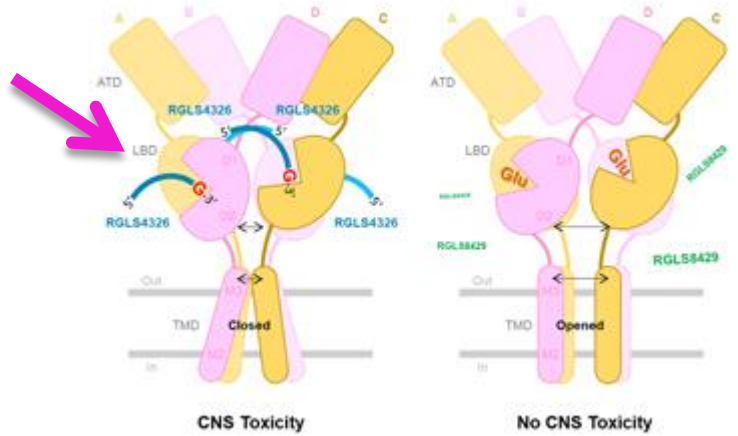
Accepted: 22 October 2025

Published online: 28 November 2025

Check for updates

Tania Valencia[1,7], Laura Y. Yen[2,3,7], Cindy Berman[4], Thomas Vincent[1], Scott Davis[1], Francesca Varrone[1], Jianfeng Huang[1], Jessica Mastroianni[1], Morgan Carlson[1], Tate Owen[1], Amin Kamel[1], Denis Drygin[1], Garth A. Kinberger[1], Shanti Pal Gangwar[3], Maria V. Yelshanskaya[3], John Ridley[5], Robert Kirby[5], Jesus Alvarez[6], Ronak Lakhia[6], Vishal Patel[6], Alexander I. Sobolevsky[3] & Edmund C. Lee[1]





Safety, Tolerability and Pharmacokinetics.

No findings of concern identified to date

	Placebo (All) N=10	RGLS8429 (1 mg/kg) N=9	RGLS8429 (2 mg/kg) N=11	RGLS8429 (3 mg/kg) N=12	RGSL8429 (All) N=32
Any Treatment Emergent Adverse Events (TEAEs)	5 (50%)	7 (78%)	7 (64%)	9 (75%)	24 (75%)
Injection site reaction (ISR)	0	0	1	6#	7
Any Treatment Related TEAEs	0	1 (11%)	5 (46%)	5 (42%)	12 (38%)
Any Treatment Emergent Serious Adverse Events (TESAEs)	0	1 (11%)*	0	0	1
Any Treatment Related TESAEs	0	0	0	0	0
Any TEAEs leading to early withdrawal	0	0	1 (9%)	2 (17%)	3

ISRs were the only TEAEs occurring in more than 2 subjects in any cohort and more frequent at 3 mg/kg but did not limit dosing

Genome editing
Για Μεσογειακή – Δρεπανοκυτταρική

Παρακολούθηση για 10 έτη μετά την γενετική παρέμβαση

Άπω νεφρικό σωληναριακό κύτταρο

•2026 May 2;53(1):707.
doi: 10.1007/s11033-026-11872-1.

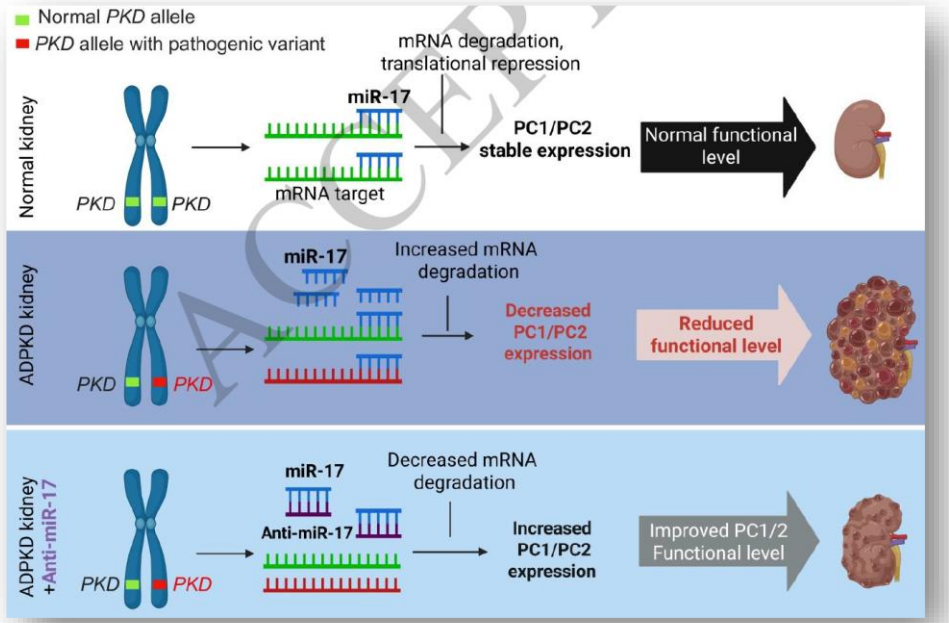
Miniaturization of CRISPRa plasmids for efficient delivery into renal epithelial cells and Pkd1 transactivation

Anubhav Chakraborty[1], Alan S L Yu[2]
Affiliations
•PMID: 42068455
•DOI: 10.1007/s11033-026-11872-1

Table 4: Gene-Based Therapeutic Strategies Under Development for ADPKD

Strategy	Vector footprint	Edit/cargo scope	Kidney deliverability (today)	Durability	Development status in ADPKD
cDNA transgene ("augmentation")	Large (PKD1 ~13 kb)	Mutation-agnostic	Challenging (cargo > AAV)	High (episomal/long-term)	Concept with mini-PC1 variants emerging
CRISPRa (gene up-regulation)	Small	Mutation-agnostic (dosage)	Plausible with AAV/LNP	Potentially durable	Preclinical
Base editing	Medium (dual-AAV typical)	Point mutations (subset)	Feasible in organoids; in vivo delivery evolving	Durable	Preclinical (organoid correction)
Prime editing	Large (split systems)	Broad edits (≤~50 bp)	Capsid/LNP engineering needed	Durable	Preclinical (other organs); renal adapting
Anti–miR-17 ASO	Small (single oligo)	Mutation-agnostic (dosage)	Favorable renal exposure	Redose	Clinical (Ph1b)
ERSGs / SSOs	Small	Nonsense or splicing variants	Feasible	Redose	Early clinical/ PoC

cDNA: Complementary Deoxyribonucleic Acid, **PKD1**: Polycystic Kidney Disease 1 gene, **kb**: Kilobase, **AAV**: Adeno-Associated Virus, **CRISPRa**: Clustered Regularly Interspaced Short Palindromic Repeats Activation, **LNP**: Lipid Nanoparticle, **ASO**: Antisense Oligonucleotide, **ERSG**: Exon Retention Small Gene, **SSO**: Splice-Switching Oligonucleotide, **PoC**: Proof of Concept, **Ph1b**: Phase 1b.

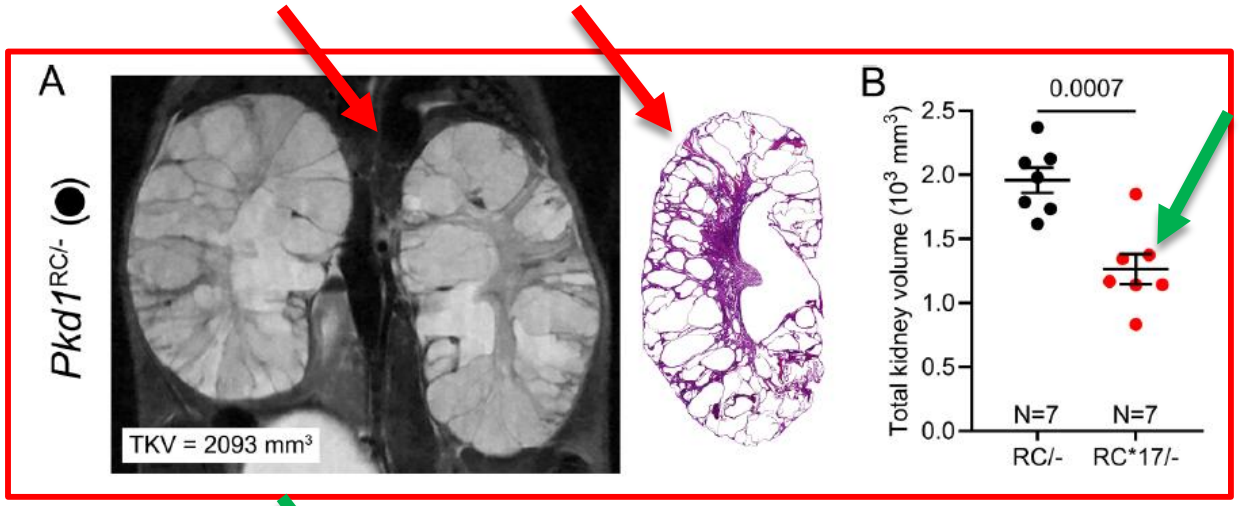


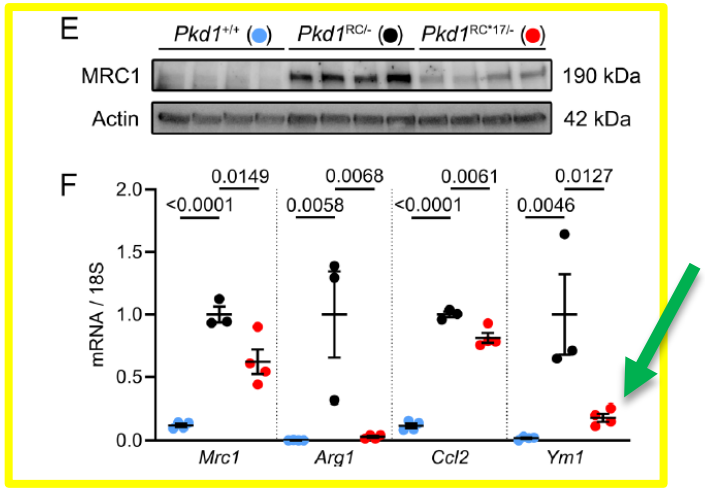
Emerging Therapies in Autosomal Dominant Polycystic Kidney Disease

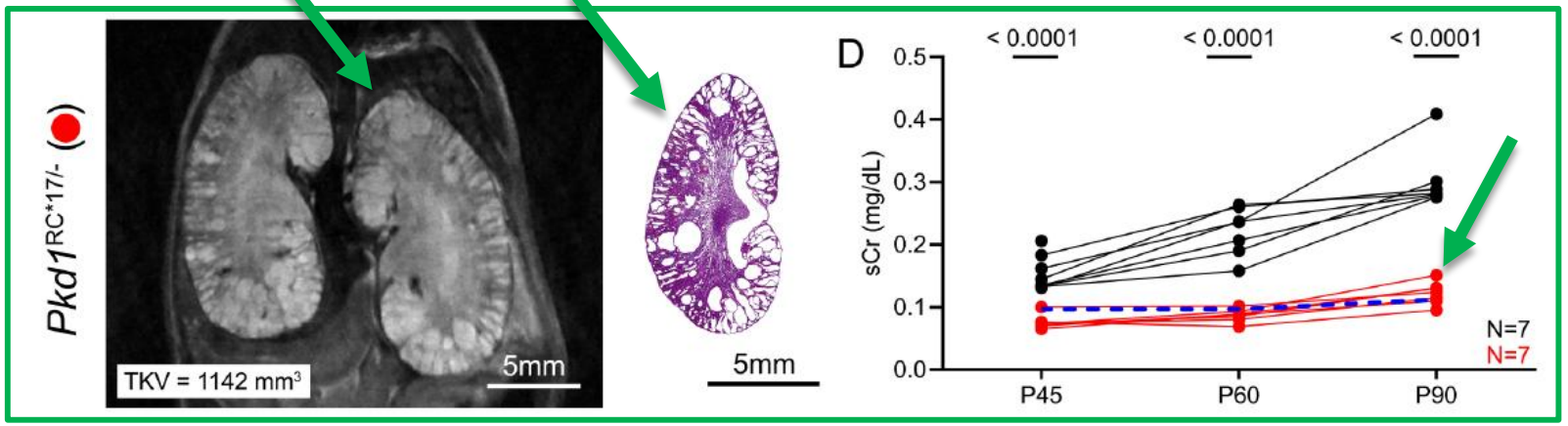
Chen, Christopher Y.[1,a]; Hadla, Mohamad[2]; Khambati, Ibrahim[2]; Kashyap, Sonu[3]; Westerfield, Vanessa[1]; Fedeles, Sorin[4]; Besse, Whitney[5]; Hopp, Katharina[6]; **Harris, Peter C.[7]; Patel, Vishal[8];** Chini, Eduardo[3]; Salih, Mahdi[9]; Barry, Michael A.[10]; Chebib, Fouad T.[2,a]

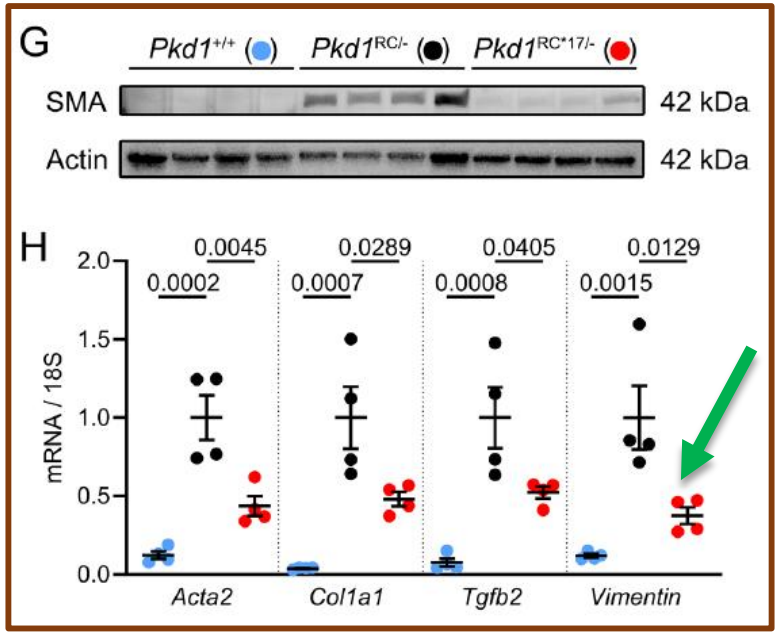
Kidney360 ():10.34067/KID.0000001109, December 12, 2025. | *DOI:* 10.34067/KID.0000001109

Pkd1 RC ∗17 substitution results in durable suppression of disease progression.









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Disruption of a six-nucleotide miRNA motif improves *PKD1* dosage and ameliorates polycystic kidney disease

Ronak Lakhia*,†, Chunzi Song†, Laurence Biggers, Maggie Zumwalt, Jesus Alvarez, Arvind Somasundaram, Harini Ramalingam, Patricia Cobo-Stark, Vishal Patel

Department of Internal Medicine and Division of Nephrology, UT Southwestern Medical Center, Dallas, TX 75390, United States

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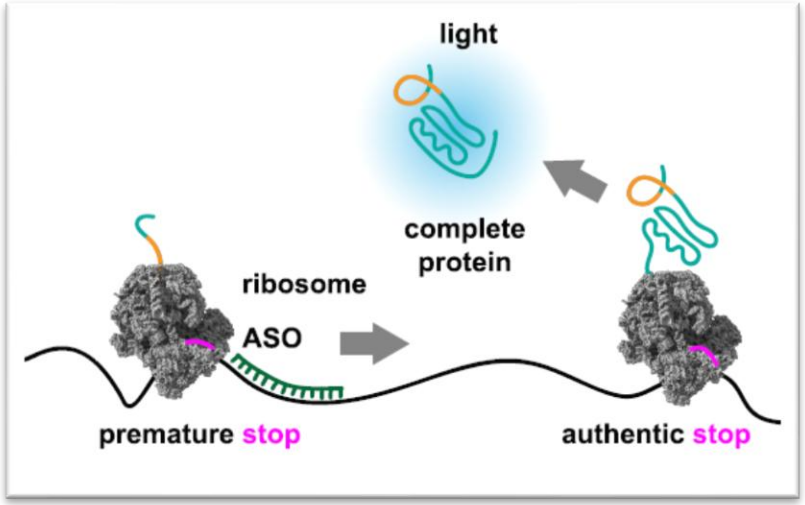
†These authors contributed equally.



Nucleic Acids Research, 2024, **52**, 8687–8701
https://doi.org/10.1093/nar/gkae624
Advance access publication date: 16 July 2024
Chemical Biology and Nucleic Acid Chemistry

mRNA-specific readthrough of nonsense codons by antisense oligonucleotides (R-ASOs)

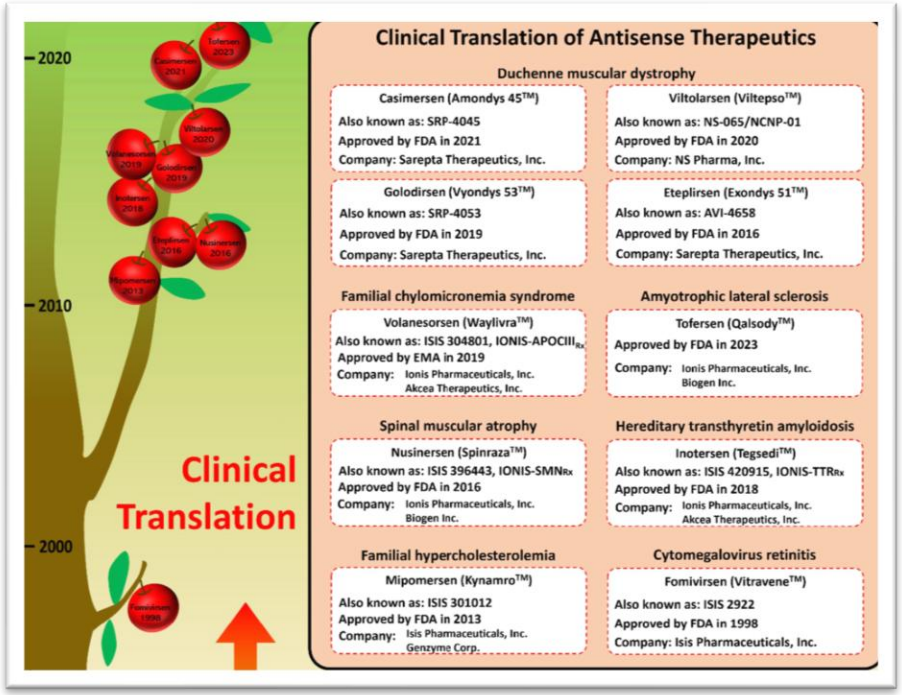
Denis Susorov, Dimas Echeverria, Anastasia Khvorova* and Andrei A. Korostelev*

RNA Therapeutics Institute, UMass Chan Medical School, 368 Plantation Street, Worcester, MA 01605, USA

*To whom correspondence should be addressed. Tel: +1 508 856 2353; Fax: +1 508 856 6696; Email: Andrei.Korostelev@umassmed.edu
Correspondence may also be addressed to Anastasia Khvorova. Tel: +1 774 455 3638; Fax: +1 508 856 6696; Email: Anastasia.Khvorova@umassmed.edu

These therapies promote **full-length protein production** by allowing the ribosomal machinery to "readthrough" the premature termination codons caused by nonsense mutations.

"As research progresses, r-ASOs could become a pivotal tool in **readthrough therapies**, though their use in **improving PKD therapy** remains to be seen."



Prospects for Gene Therapy in Polycystic Kidney Disease

Chakraborty, Anubhava, Yu, Alan S.L.
The Jared Grantham Kidney Institute, University of Kansas Medical Center, Department of Cell Biology and Physiology

Current Opinion in Nephrology and Hypertension
Published ahead of print

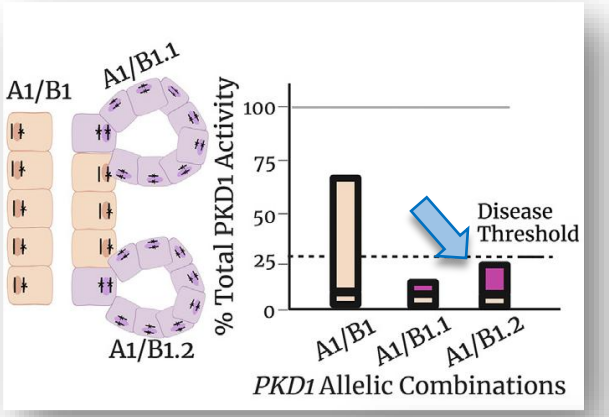
↓ Polycystin-1 and -2 dosage within individual tubular epithelial cells

↓

Aberrant cellular signaling:
↑ cAMP, ↑ mTOR, ↑ ERK,
↑ JAK-STAT, ↓ AMPK

↓

↑ Clonal expansion of epithelial cells
Cyst formation and growth

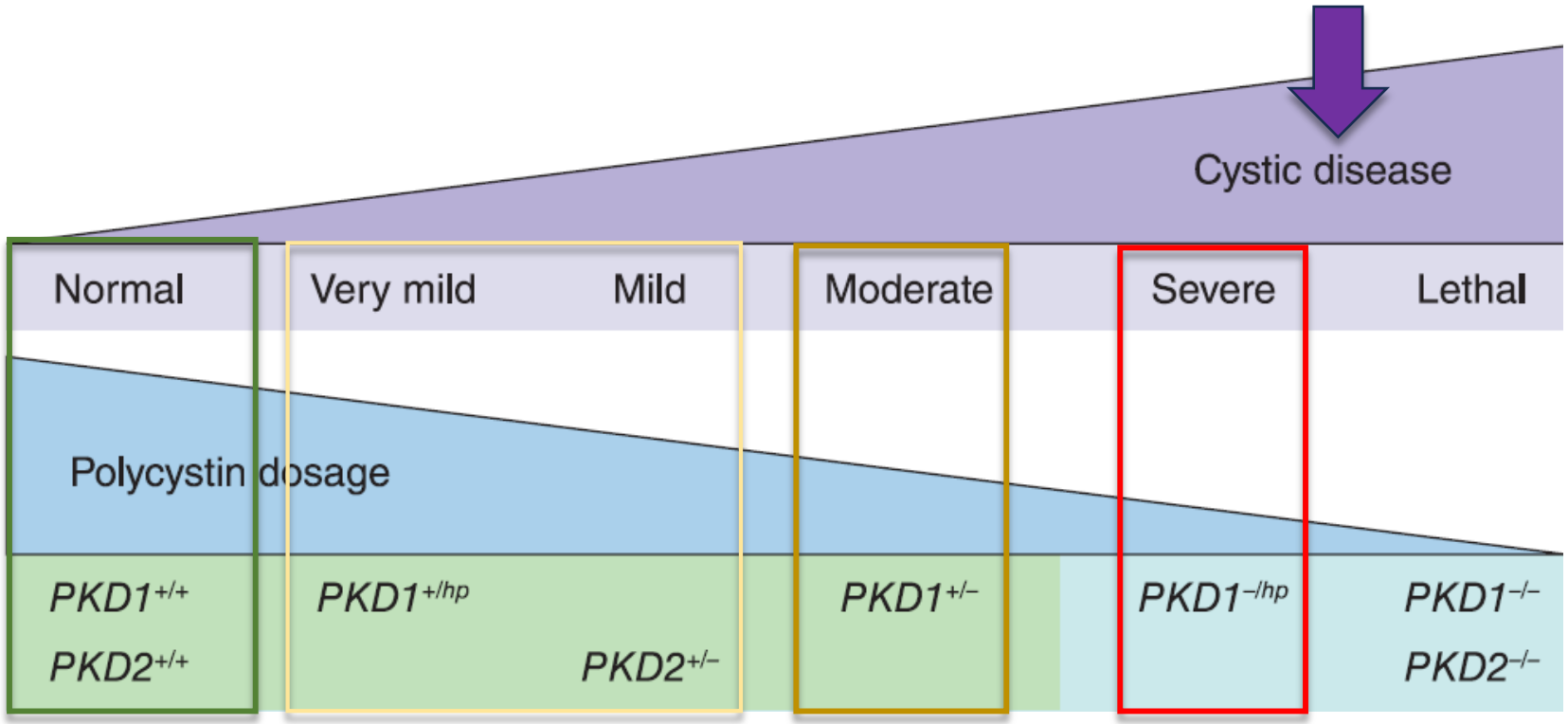


AKDH

Mechanisms of Cyst Development in Polycystic Kidney Disease

Jiahe Qiu, Gregory G. Germino, and Luis F. Menezes

functional polycystin dosage and cystic disease severity.



hp, hypomorphic variant.

Insights into Autosomal Dominant Polycystic Kidney Disease from Genetic Studies

Matthew B. Lanktree,[1] Amirreza Haghighi,[2] Ighli di Bari,[2] Xuewen Song,[2] and York Pei[2]

www.cjasn.org Vol 16 May, 2021

Γιατί είναι αναγκαία η γενετική θεραπευτική στην Πολυκυστική νόσο των νεφρών (ΠΚΝ) ?

Θα είναι αποτελεσματική και χωρίς παρενέργειες ?

Ποιες γενετικές ιδιαιτερότητες υπάρχουν στην ΠΚΝ ?

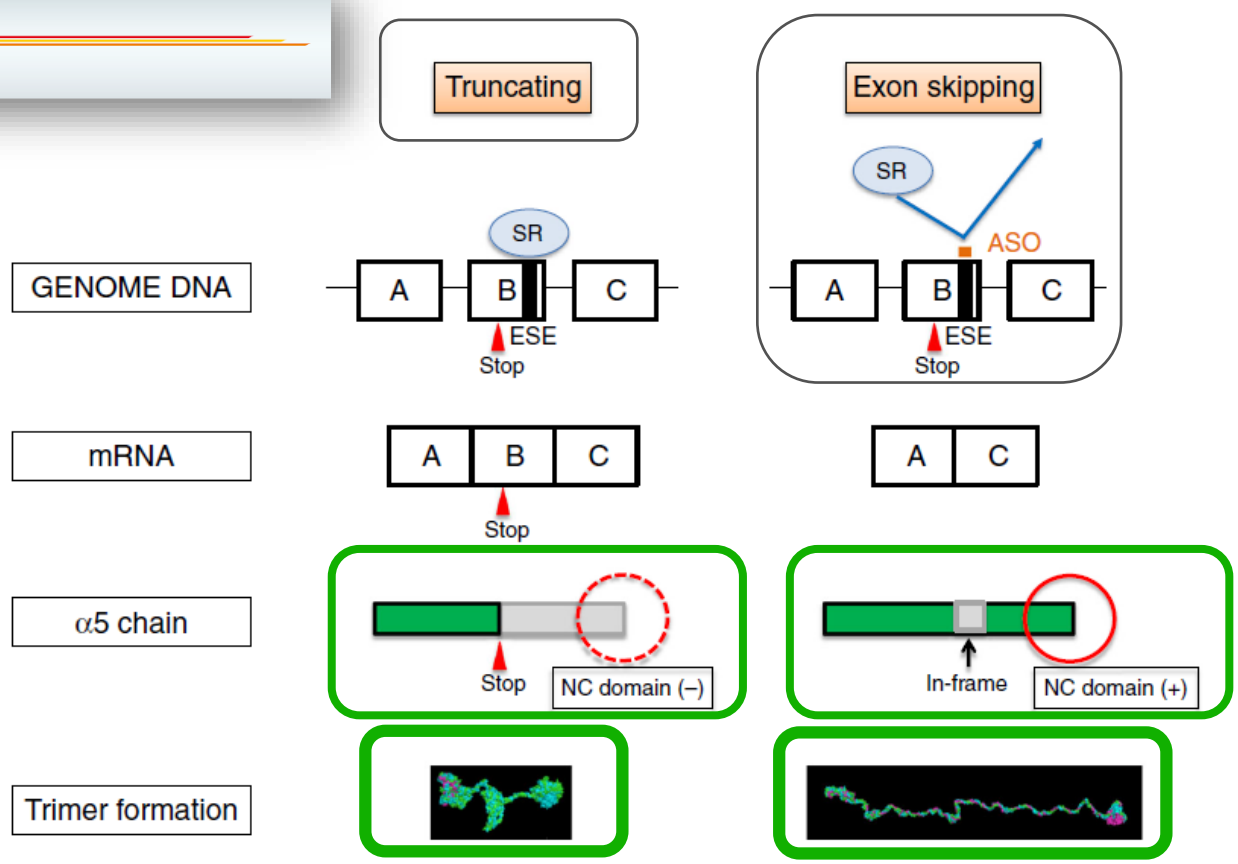
Σε ποιο σημείο των γενετικών δρόμων μπορούμε να παρέμβουμε και πως?

Τι δεδομένα υπάρχουν μέχρι σήμερα από τις παρεμβάσεις μας?

Τι να περιμένουμε και πως θα χειριστούμε τα δεδομένα και τα αποτελέσματα μιας κλινικής μελέτης φάσης 3 με γενετική παρέμβαση στη ΠΚΝ?

Ποιες περαιτέρω δυνατότητες γενετικής επεξεργασίας έχουμε και πως μπορούμε να τις εφαρμόσουμε σε επίπεδο νεφρών?

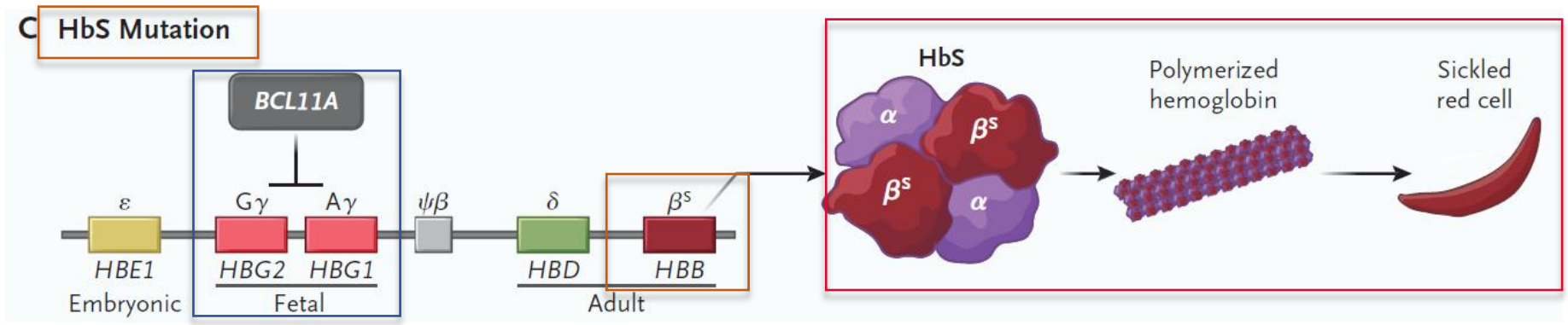
nature COMMUNICATIONS

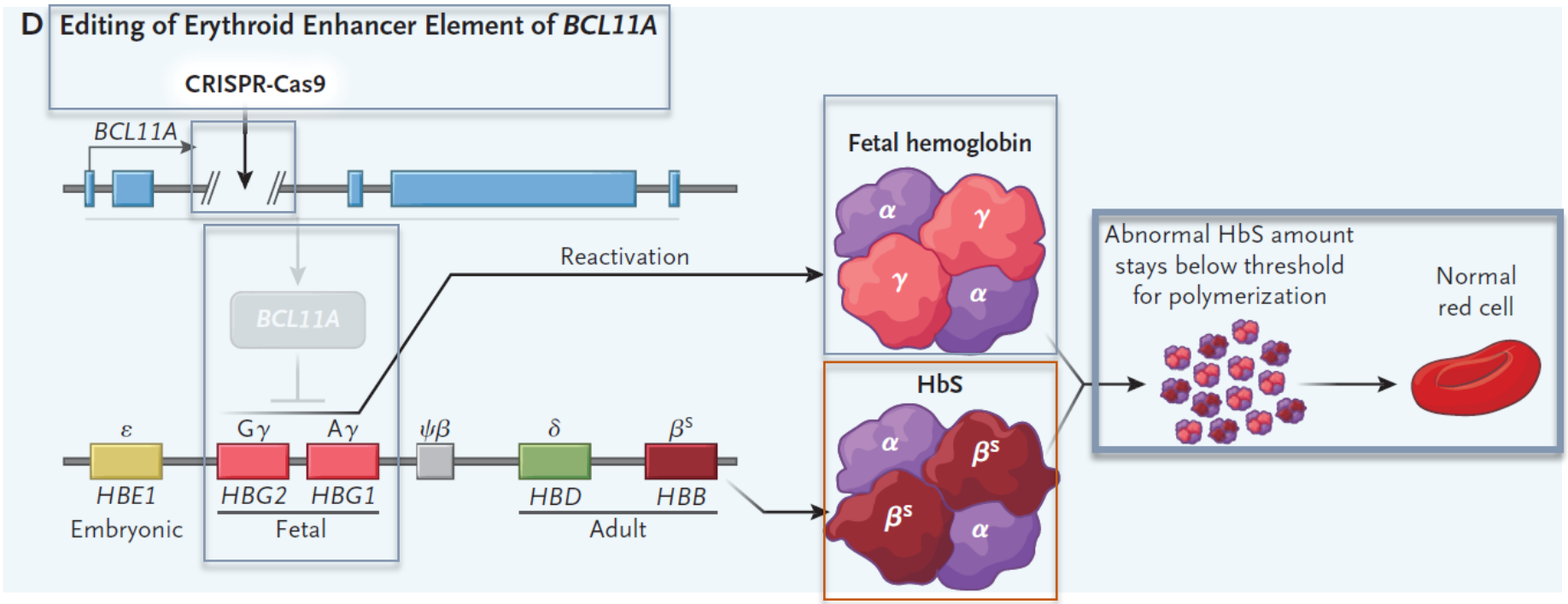


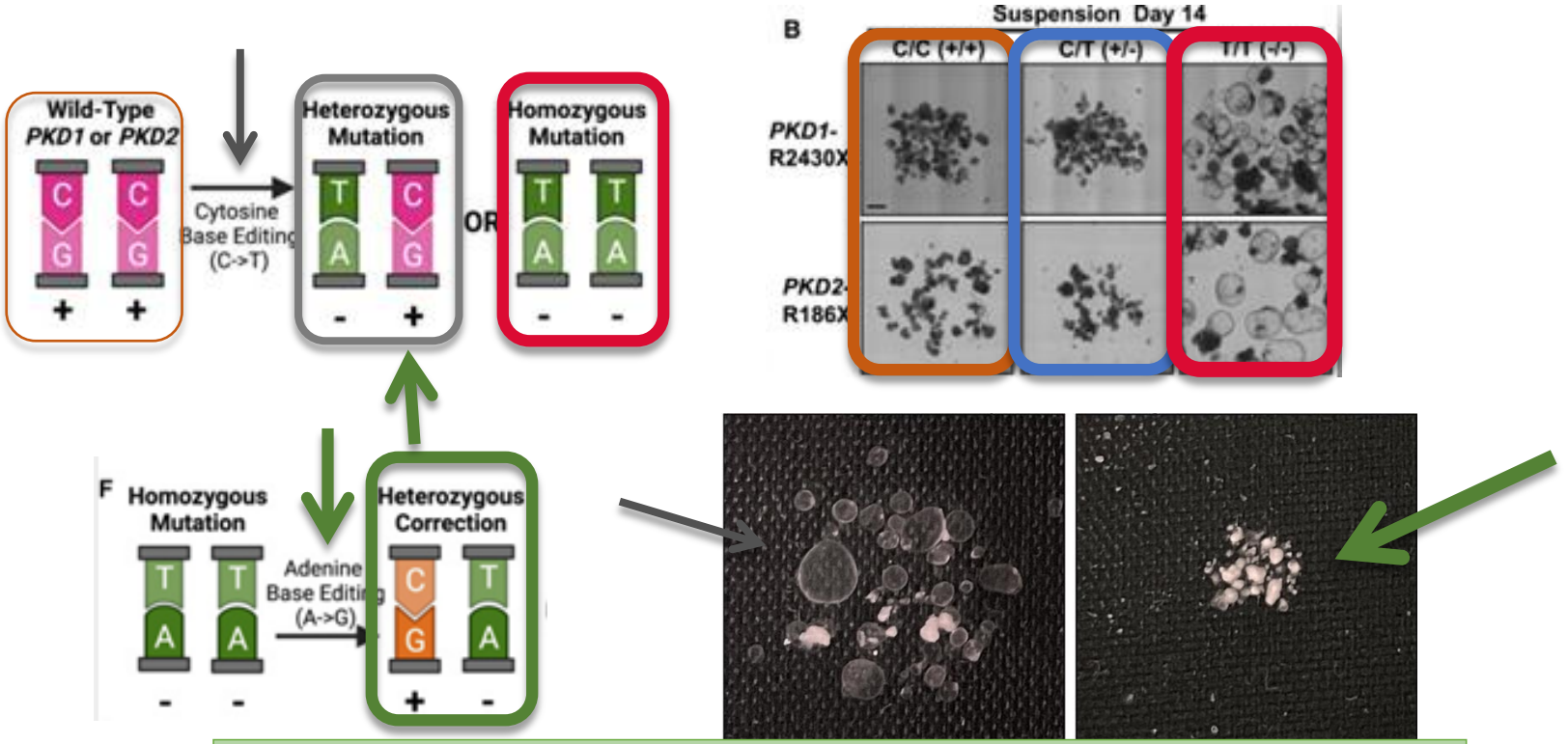
With the **truncating variants** in **COL4A5**, the type collagen α5 chain will terminate at the stop codon and the NC1 domain is missing (left panel).
In contrast, exon-skipping therapy will replace the truncating variant with **an in-frame deletion variant** at the transcript level and the NC domain is not lost

Development of an exon skipping therapy for X-linked Alport syndrome with truncating variants in COL4A5

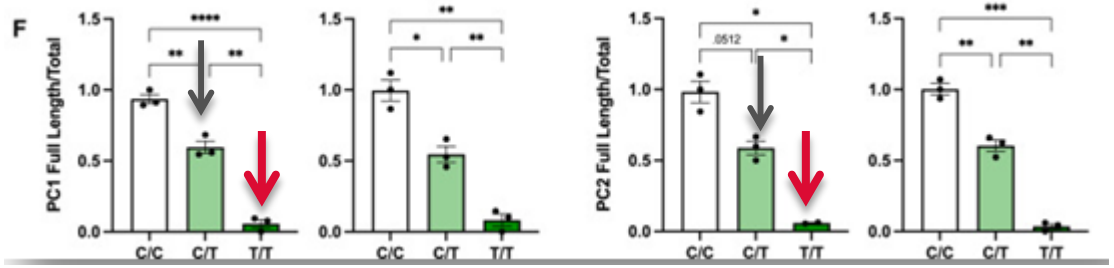
NATURE COMMUNICATIONS | https://doi.org/10.1038/s41467-020-16605-x

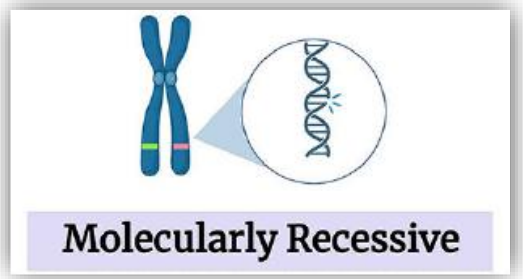

C HbS Mutation
BCL11A
ε
Gγ
Aγ
ψβ
δ
βS
HBE1
HBG2
HBG1
HBD
HBB
Embryonic
Fetal
Adult
HbS
Polymerized hemoglobin
Sickled red cell


D Editing of Erythroid Enhancer Element of BCL11A
CRISPR-Cas9
BCL11A
Reactivation
Fetal hemoglobin
HbS
Abnormal HbS amount stays below threshold for polymerization
Normal red cell
ε
Gγ
Aγ
ψβ
δ
βS
HBE1
HBG2
HBG1
HBD
HBB
Embryonic
Fetal
Adult



Base editing can constitute a viable therapeutic strategy for PKD





Genetics of cystogenesis in base-edited human organoids reveal therapeutic strategies for polycystic kidney disease

Courtney E Vishy[1], Chardai Thomas[1], Thomas Vincent[1], Daniel K Crawford[2], Matthew M Goddeeris[2], Benjamin S Freedman[3]