Aleixo Muise MD PhD FRCPC

Canada Research Chair in Pediatric IBD (Tier 1)
SickKids IBD Centre
Program in Cell Biology,
Research Institute, Hospital for Sick Children,
Departments of Paediatrics and Biochemistry,
University of Toronto

SickKids® | Inflammatory Bowel Disease Centre

UNIVERSITY of TORONTO

Disclosure

- I have nothing to disclose.

- Industry
  - Collaborative project with Regeneron Pharmaceutical - provides in-kind sequencing (no funding or individual or lab payments).

- Research Grants
  - Helmsley Charitable Trust, CIHR, NIH, Canada Research Chair.

- Trainee Funding
  - SickKids (Restracomp), CIHR, CAG, CCC.

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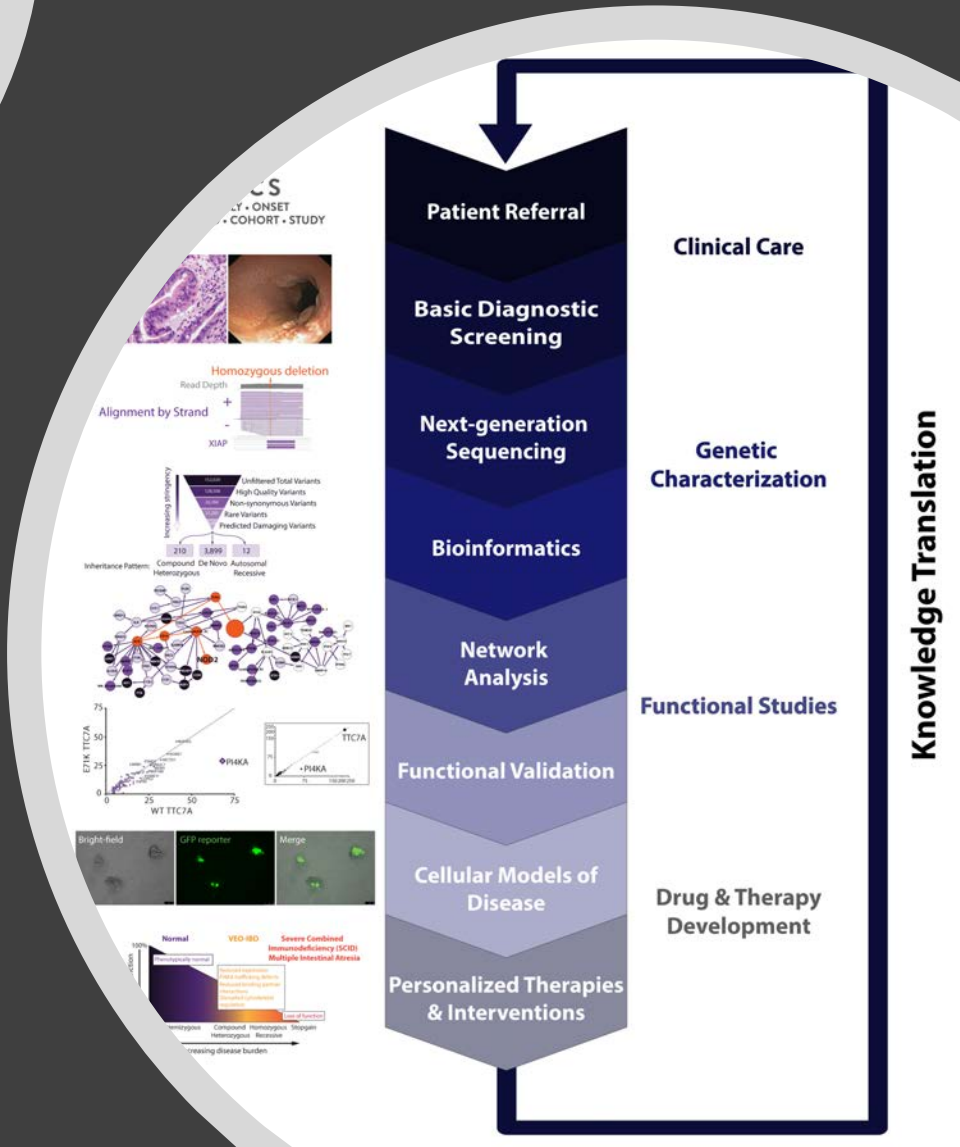
Program Goal

1. to help treat children from SickKids and around the world

2. to develop genetic/omics/functional approaches to treat patients

"PRECISION MEDICINE"



Precision IBD Care

“approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."

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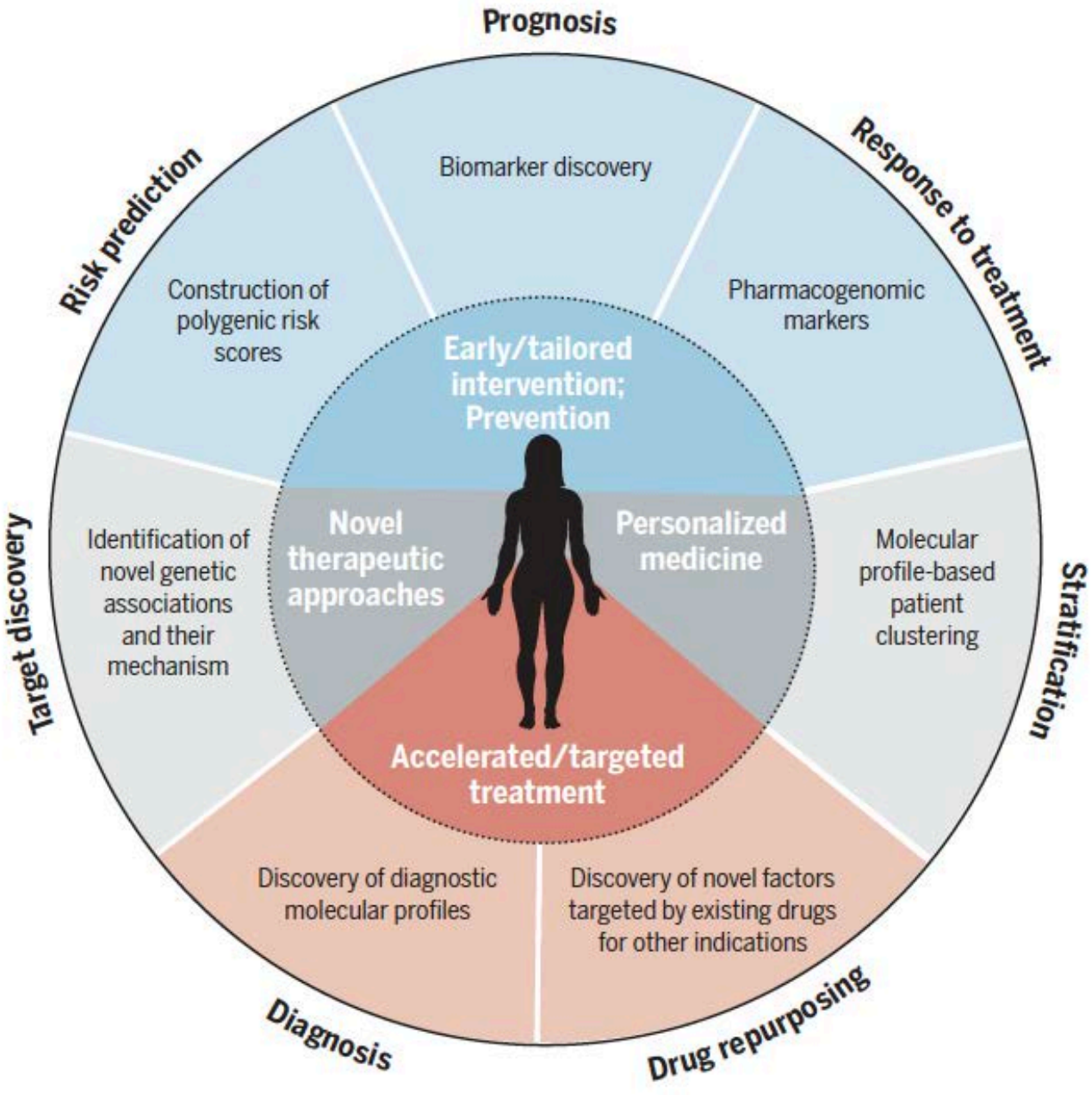

Zeggini et al., Science 365, 1409–1413 (2019)

Some factors driving Precision IBD Care in Pediatrics

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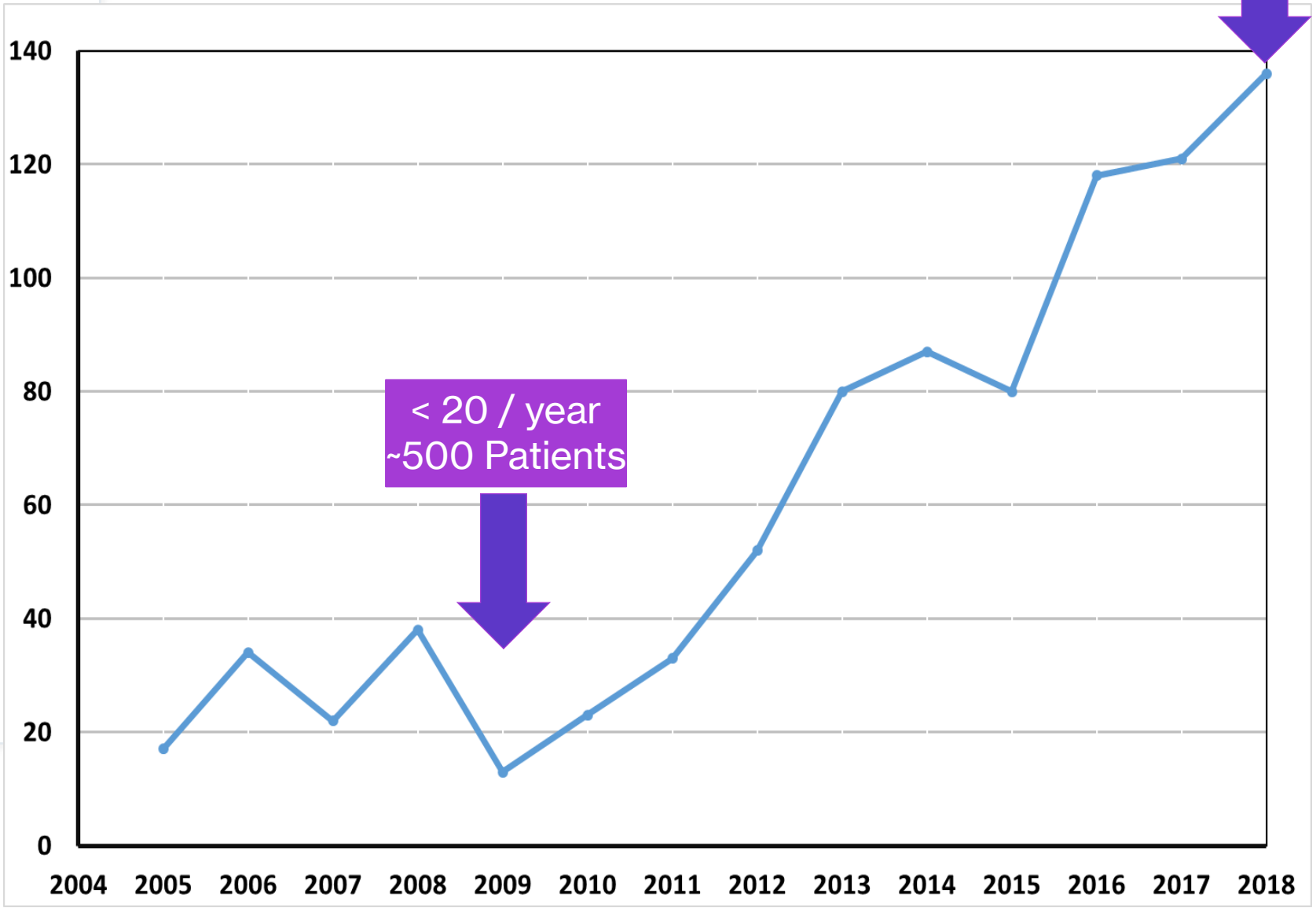
Number of Pediatric IBD patients diagnosed per year at SickKids, Toronto.

2006-2018.

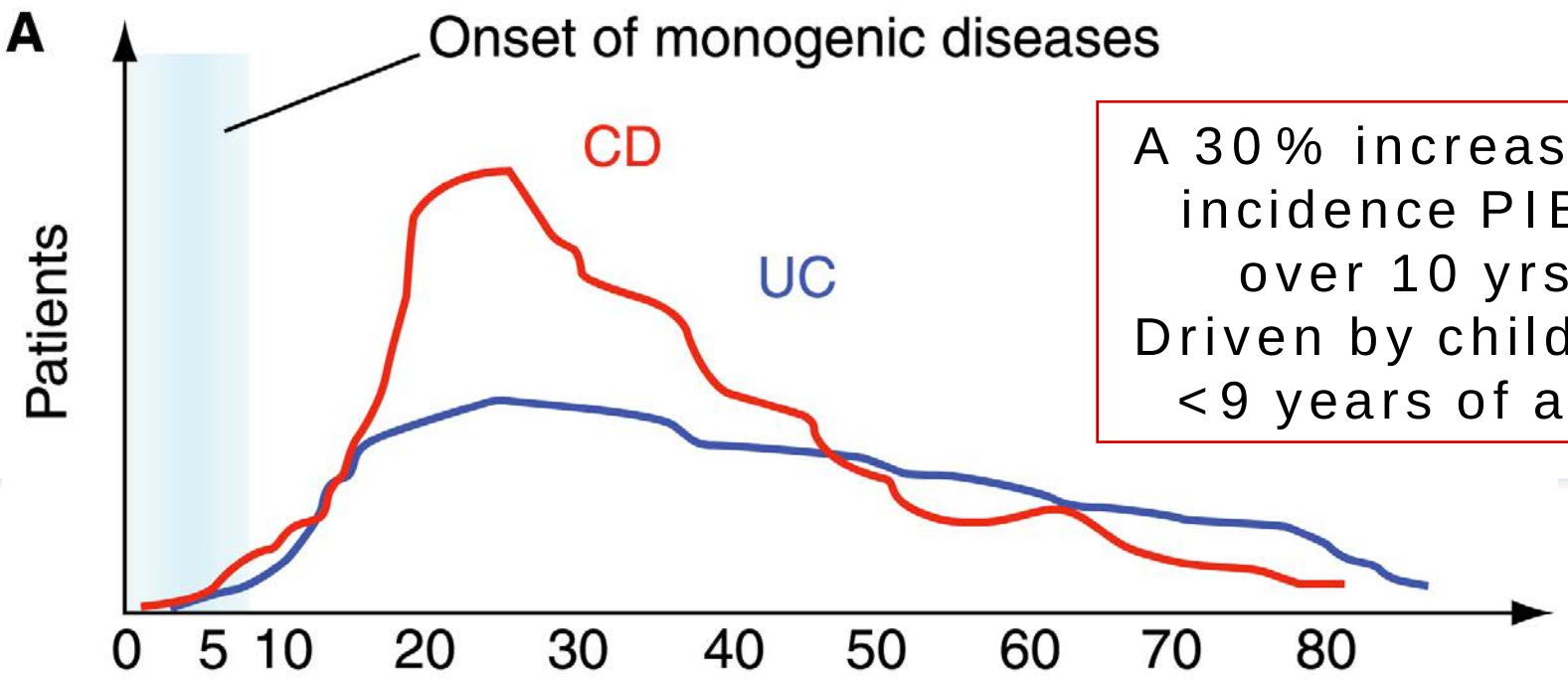
Crowley, Griffiths, Muise et al. ESPGHAN 2019



What is driving the increase in IBD incidence: IBD is NOW a Pediatric Disease

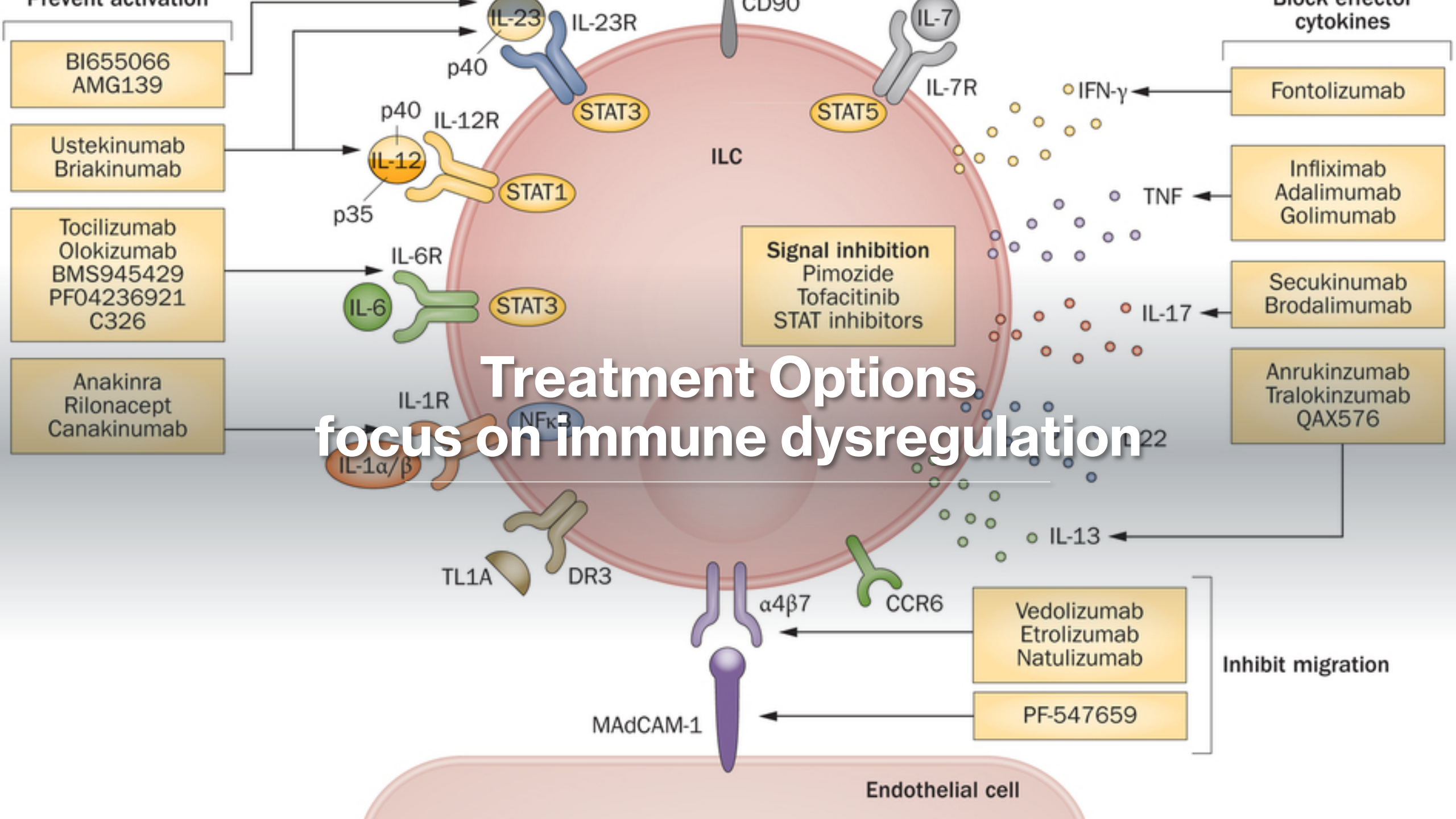
Shift in Incidence to Pediatric Age Group

kids dx <6 years of age most likely NOT monogenic



A 30% increase in incidence PIBD over 10 yrs Driven by children <9 years of age

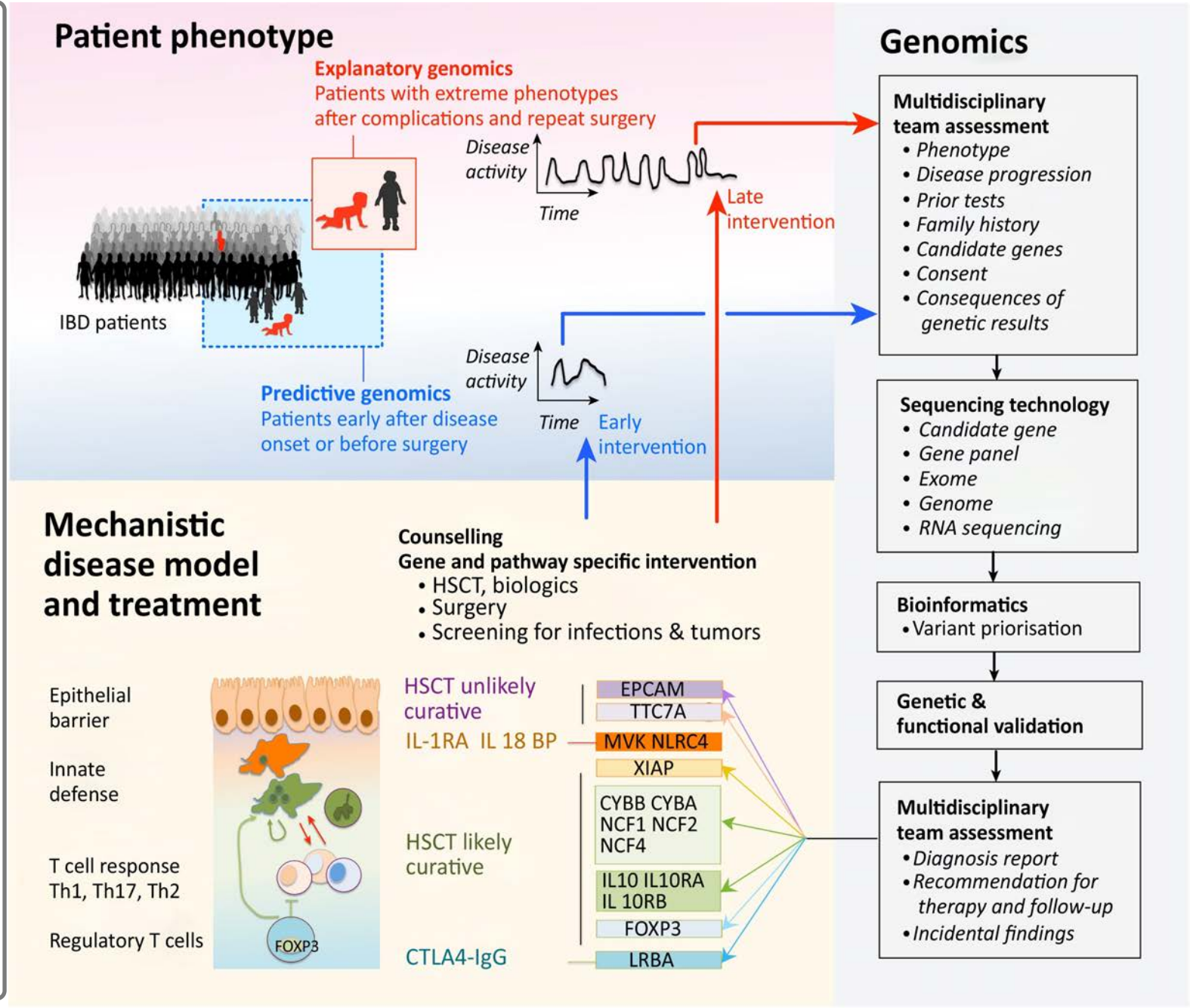
Modified from Uhlig Gut, 2013



Treatment Options focus on immune dysregulation

Our Approach to Precision Medicine

Use of genetics to determine clinical care



Uhlig and Muise – Trends in Genetic, 2017

Making the correct diagnosis –
Genetics diagnosis from ~ 100 kids from across Canada and around the world

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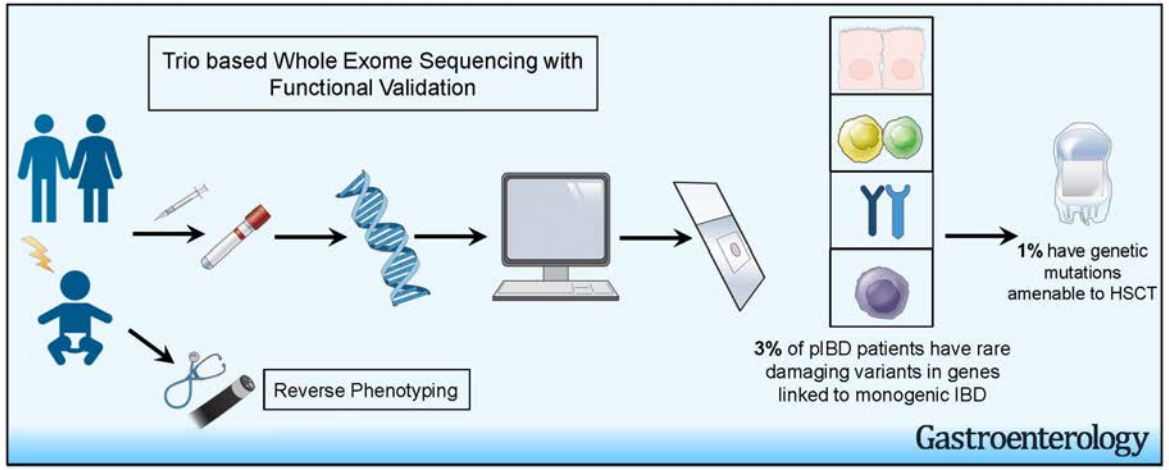
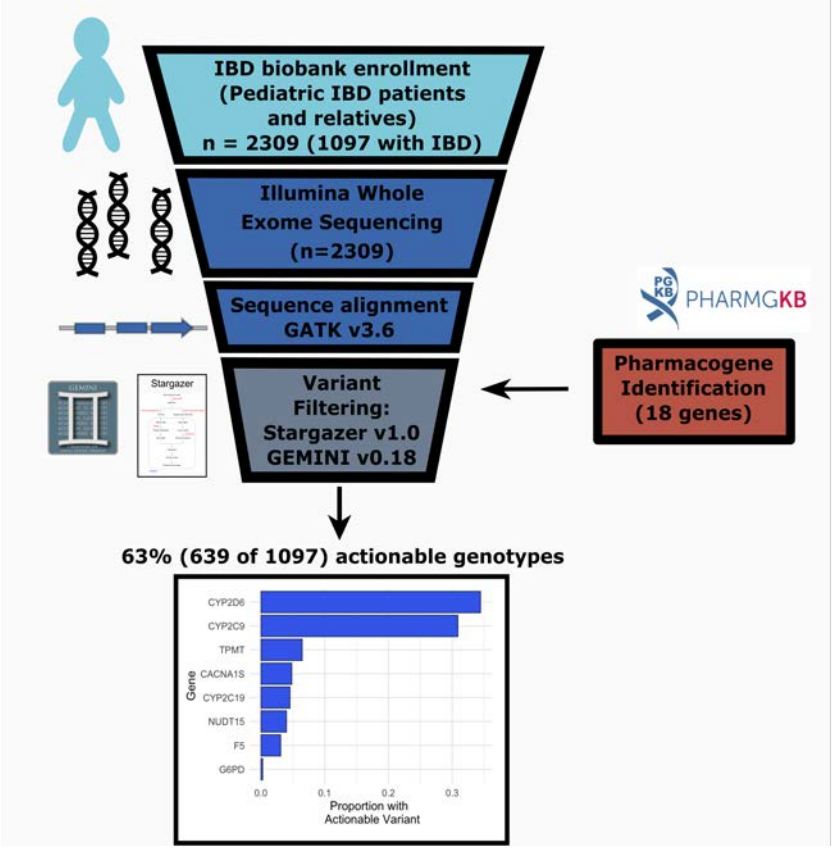
Next Generation Sequencing in IBD

WES - 1005 SickKids IBD Patients (all ages)





Monogenic IBD ~ 3-5% of all IBD
Crowley et al Gastroenterology, 2020

Pharmacogenomics ~ 63% of Patients
Mulder et al CTG, 2020

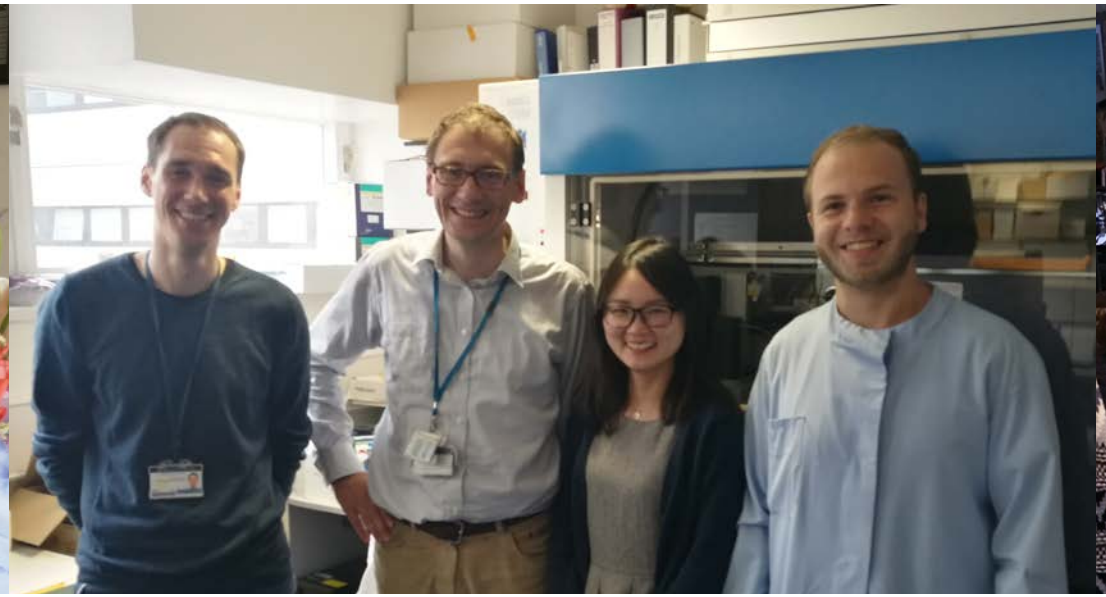
New Diseases: Novel Therapeutic Targets

Novel VEOIBD Genes – therapies

5-year Collaborative Project
Shanghai-Toronto-Oxford

collaborators in Canada, China, UK, Israel, Germany, Austria, Hungary, US, and Hong Kong

Lin Wang (PhD - Muise Lab 2015-17) with Ying Huang, Fudan

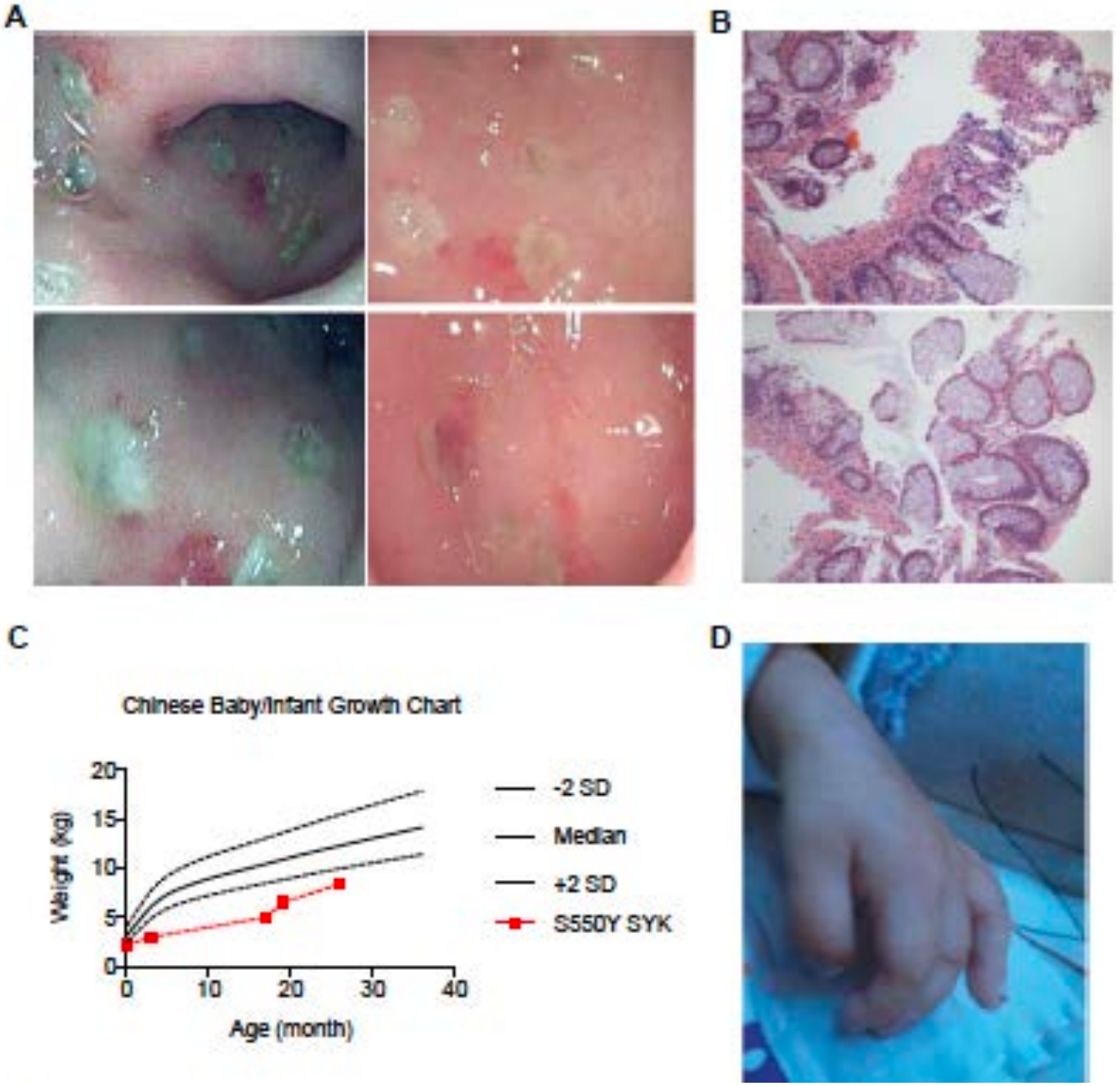


Lin and Uhlig Team – Oxford

Ying Huang, Fudan Children's Hospital, Shanghai China

Patient 1 - **Li Jiaying**

- Female patient of Chinese ancestry
- Healthy non-consanguineous parents
- Presented at 2 weeks of age with fever, whole body rash, and non-bloody diarrhea (5-8 times per day)
- Upper and lower gastrointestinal endoscopy at 2 months
  - multiple ulcers in the descending colon, sigmoid colon, and rectum
  - histology showed a chronic non-specific inflammation
- At 17 months of age developed:
  - perianal fistulas, severe colitis
  - arthritis, joint pain, swelling on her hands
  - recurrent pulmonary infections
  - significant growth failure
- Passed away before her 3rd birthday after complications from an infection.



Lin Wang

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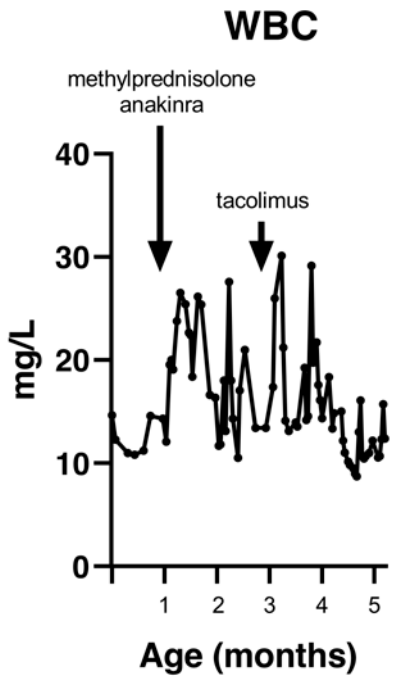
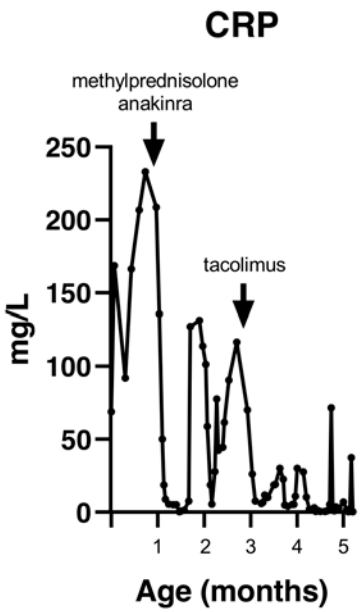
Patient 2 - MS

- Term baby (SickKids) – no complications, parents no consanguineous, Ashkenazi (dad adopted)
- Presented at 2 weeks with intermittent fever, skin rash, diarrhea, and elevated inflammatory marker
- Ear Pits, Pustular rash
- Macrophage activation Syndrome?
- Scope – showed mild colitis in cecum otherwise normal – consistent with **early onset IBD**
- **Skin bx – consistent with vasculitis**
- Elevated CRP > 200, Low IgD
- Okay growth
- 15 mos - arthritis and persistent colitis
- Failed anakinra, tacrolimus, steroids, nystatin
- Started Vedo….?

- **NO FAMLY HISTORY**…..! Delayed in identification of causal gene





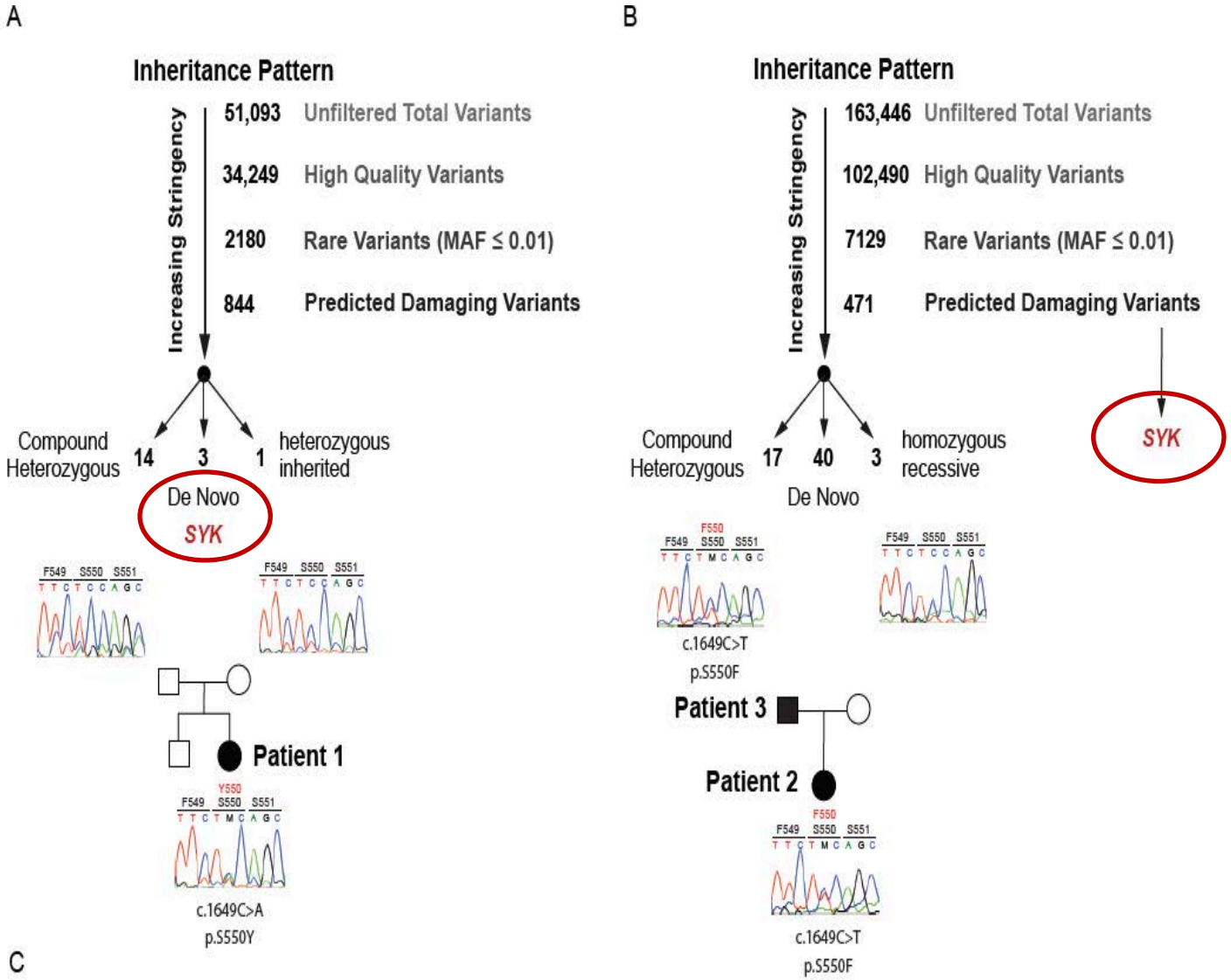
Patient 3—Father of MS

- Severe illness beginning at ***2 weeks*** of life
  - oral ulcers, fever and rash treated with antibiotics
  - progressed to prolonged diarrheal illness and anemia leading to hypernatremia and hypoalbuminemia requiring TPN, and prolonged hospitalization?? *MONTHS*
- **Dx Immunodeficiency (1980s):**
  - low T cell populations,
  - low lymphocyte mitogen stimulation,
  - low IgG levels
- **Adult:**
  - bowel, skin, joint symptoms his whole life
  - Fever with elevated CRP - monthly
  - repeated ear infections requiring surgical intervention.
  - Not normal but not severe enough for treatment

NEOPICS

gain-of-function variants

Lin Wang and Neil Warner



3 additional patients

Total: 6 patients

NEOPICS

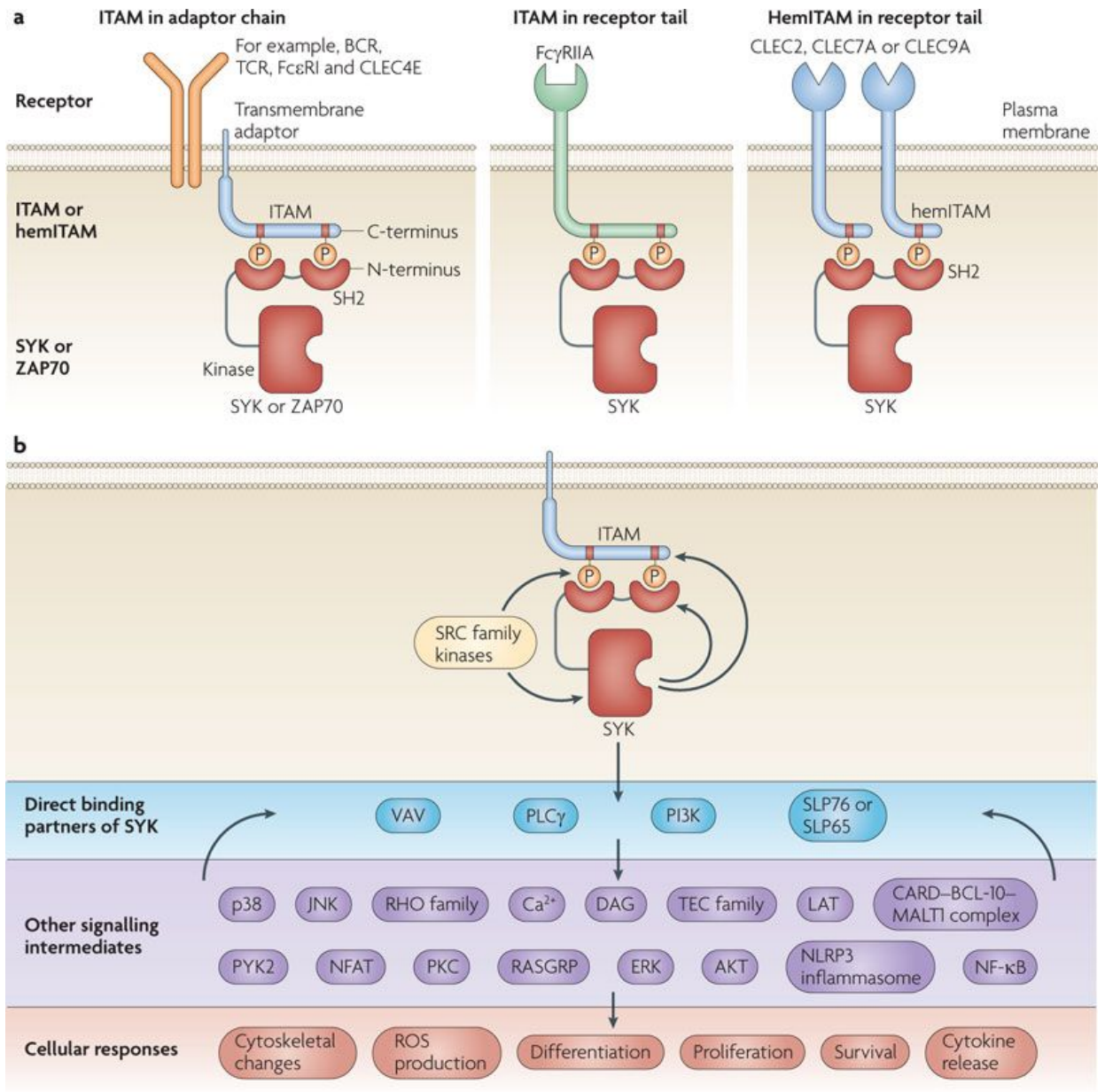
Immune dysregulation Inflammation

All had colitis

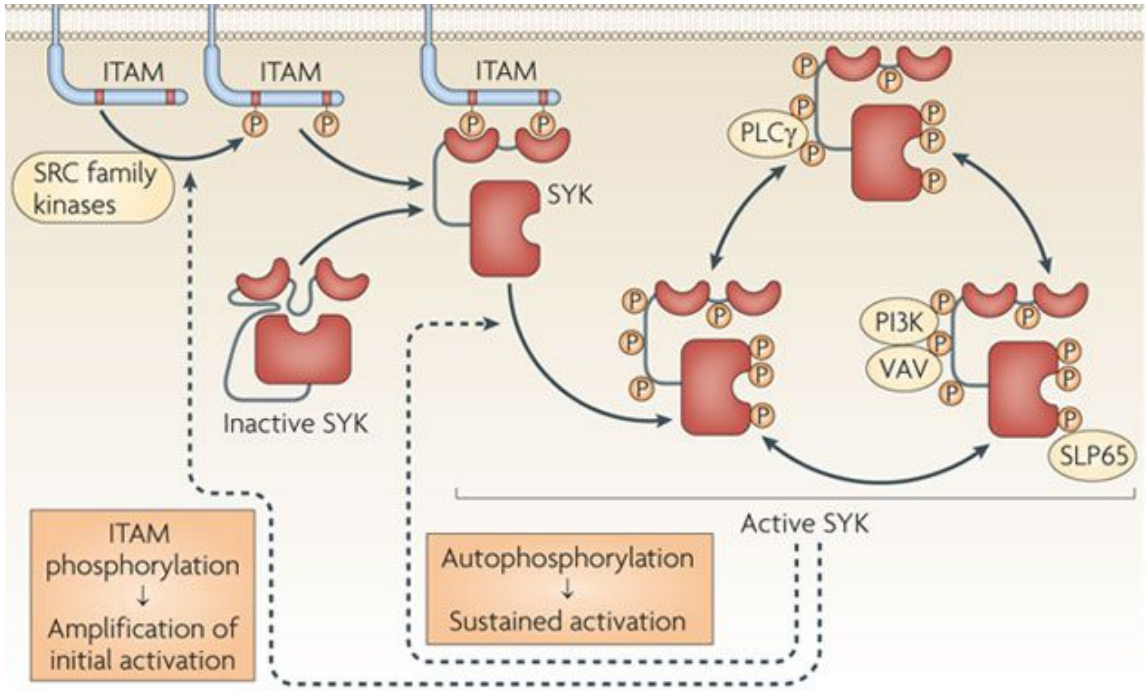
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
	p.S550Y	p.S550F	p.S550F	p.P342T	p.M450I	p.A353T
Variant Annotation						
Chromosome	9	9	9	9	9	9
positon (GRCh38)	90887816	90887816	90887816	90874692	90877739	90874725
nt ref	C	C	C	C	G	G
nt alt	A	T	T	A	A	A
dbSNP151	.	.	.	.	rs1304839707	rs200167353
pos (GRCh37)	93650098	93650098	93650098	93636974	93640021	93637007
1000Gp3_AF	.	.	.	.	.	.
ESP6500_AA_AF	.	.	.	.	.	.
ExAC_AF	.	.	.	.	.	2.47E-05
gnomAD_exomes_AF	.	.	.	.	7.95E-06	1.99E-05
COSMIC						8
CADD_phred	28.3	29.7	29.7	25.5	26.3	27.3
SIFT_pred	damaging	damaging	damaging	damaging	damaging	tolerated
Polyphen2_HDIV_pred	damaging	damaging	damaging	damaging	tolerated	damaging
LRT_pred	damaging	damaging	damaging	damaging	damaging	damaging
MutationTaster_pred	damaging	damaging	damaging	damaging	damaging	damaging
PROVEAN_pred	damaging	damaging	damaging	damaging	tolerated	tolerated
MetaSVM_pred	damaging	damaging	damaging	damaging	tolerated	tolerated
M-CAP_pred	damaging	damaging	damaging	damaging	damaging	damaging
fathmm-MKL_coding_pred	damaging	damaging	damaging	damaging	damaging	damaging
Clinical presentation						
Age at sampling (years)	2	0.5	35	31	34	44
Age of diagnosis	2 weeks	2 weeks	2 weeks	12 years	34 years	44 years#
Intestinal inflammation	+	+	+	+	+	+
Skin inflammation	+	+	+	+	+	–
Joint inflammation	+	+	+	–	–	+
Lung inflammation	–	+	–	–	+	+
CNS inflammtion	–	–	–	+	+	–
Liver inflammation	–	–	–	–	–	+
Recurrent infections	+	+	+	+	+	+
Hypogammaglobineamia	+	+	+*	+	+	+
Diffuse large B cell lymphoma (DLBCL)	–	–	–	–	+	+
Therapy (in chronological order first used)						
	ABX	ANAK	ABX	IVIG	IVIG	IVIG
	5ASA	CSTD	IVIG	CSTD	CSTD	ABX
	CSTD	TACRO	RITUX	CYCA	RITUX	
	IVIG	RITUX		AZA	CHOP	
	THAL	TRIAM		RITUX	ABX	
		VEDO				

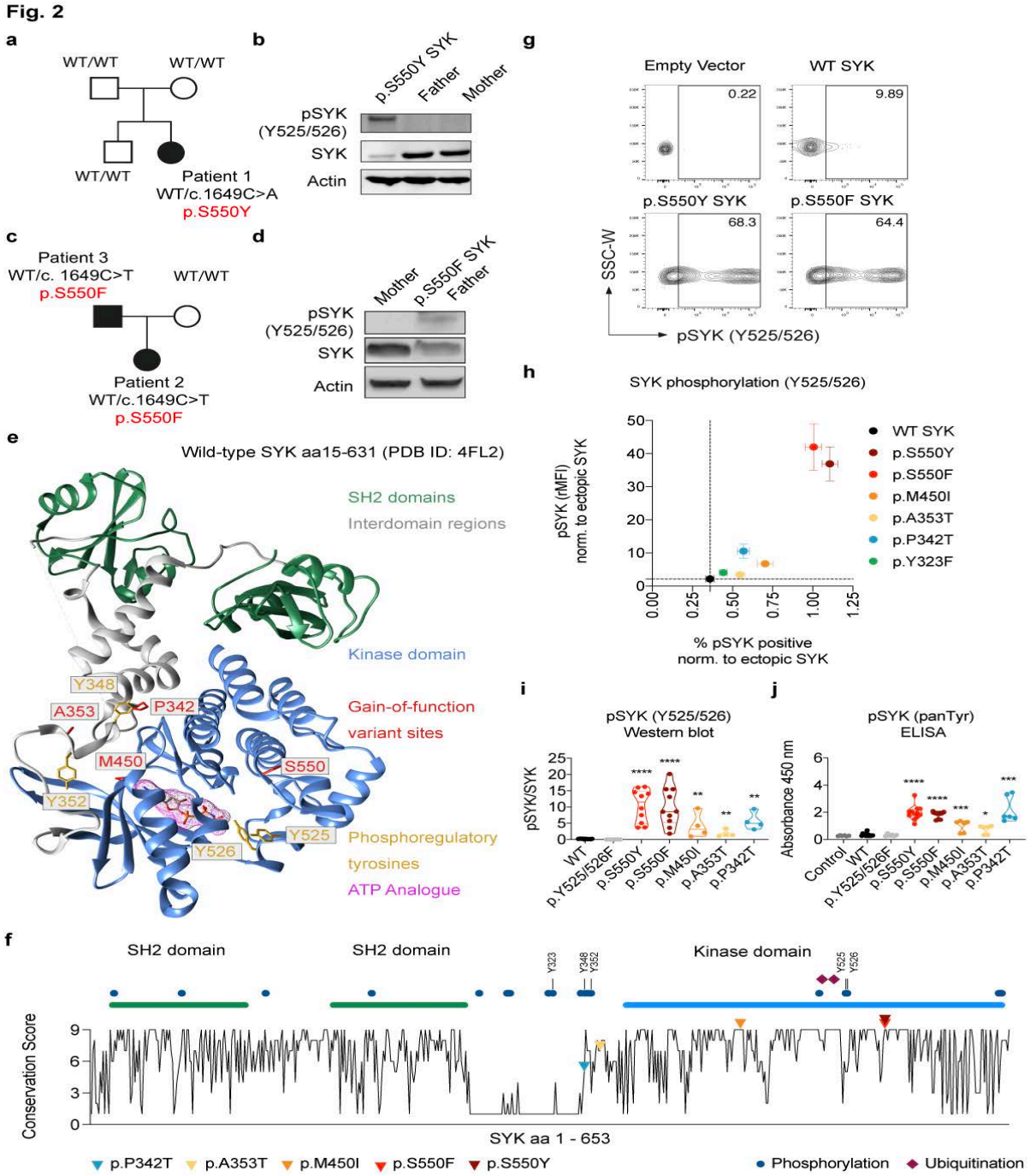
Spleen Tyrosine Kinase (SYK)

- **Adaptive** Immunity
- Immunoreceptor tyrosine-based activation motifs (ITAMs)
  - B and T cell receptors (BCR, TCR)
  - Fc receptors (FcRs)
- **Innate** Immunity
  - Innate recognition of **fungal** and other microbial pathogens
  - Dectin- SYK-CARD9–BCL10–MALT1
  - NLRP3 inflammasome activation - fungal infection
- **DRUGGABLE - allergic and autoimmune diseases and ITP**



SYK-variants all showed gain-of-function (GoF) Enhanced 525/526 Tyrosine phosphorylation

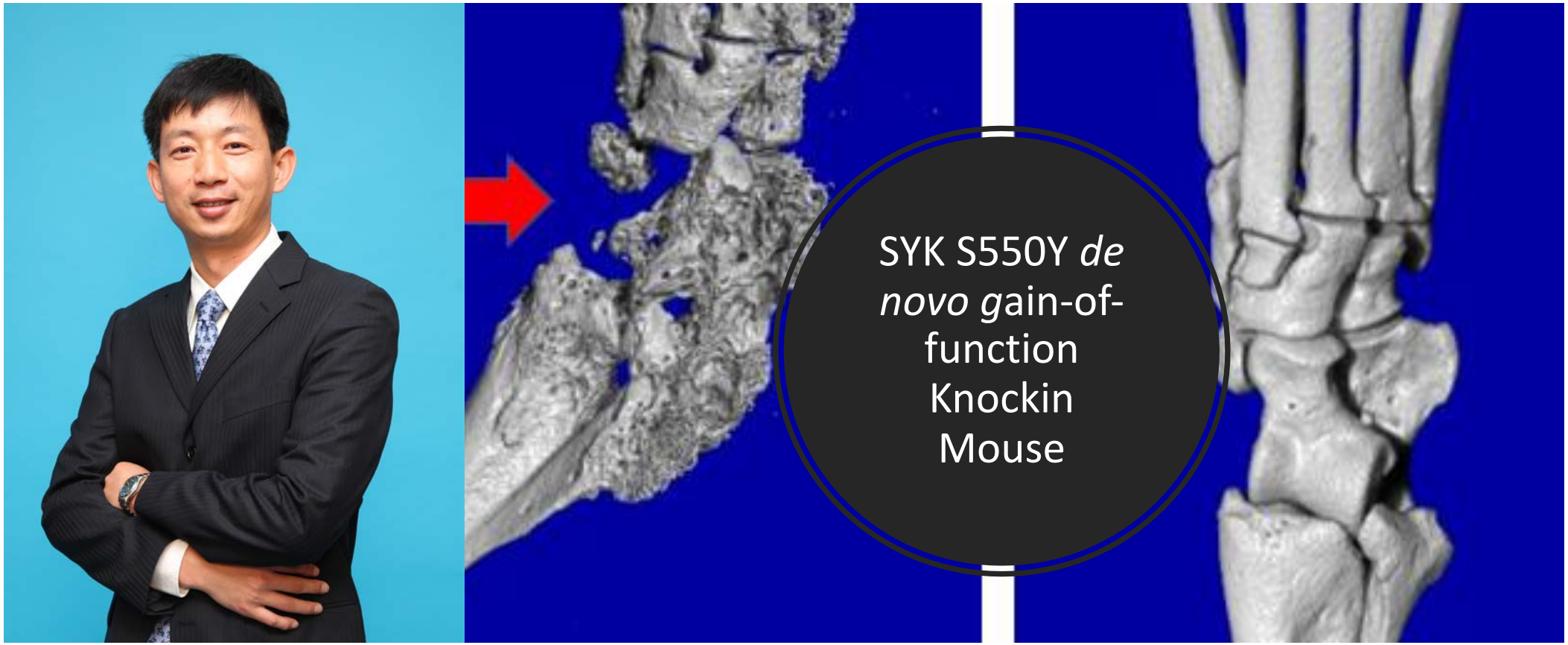




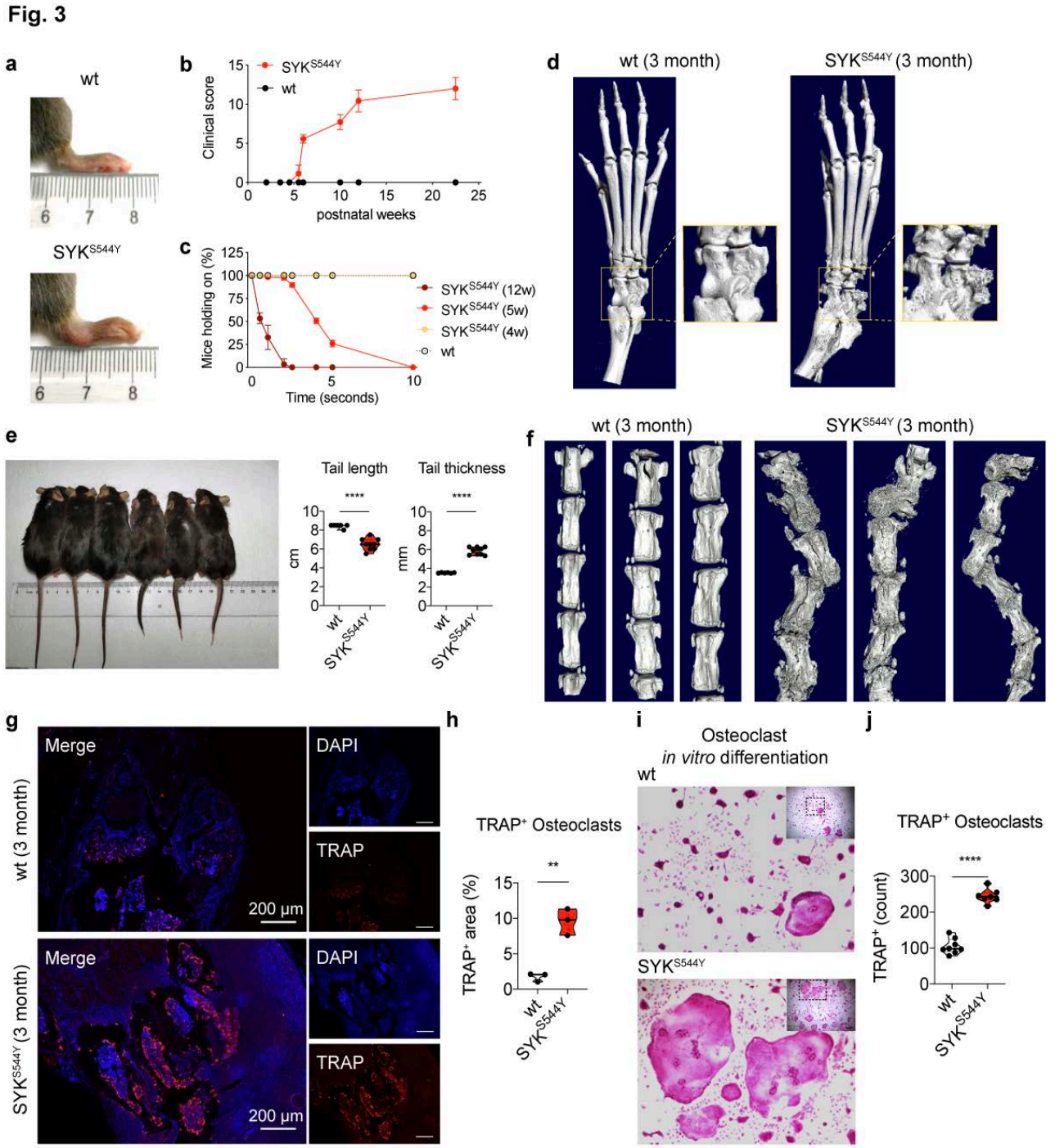
Dali Li

A CRISPR-Cas9-knockin mouse model of SYK GOF presents with spontaneous arthritis and defective B cell function

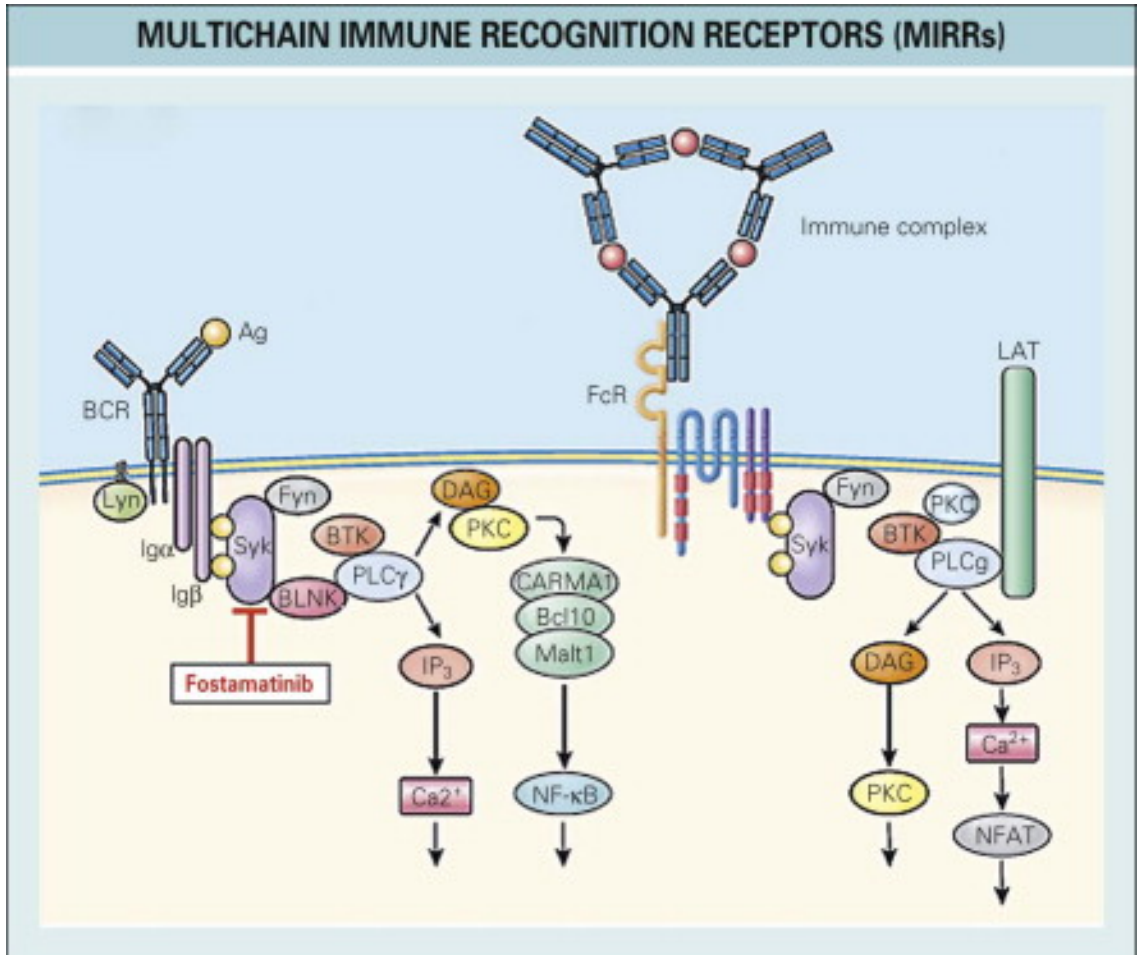
East China Normal University, Shanghai



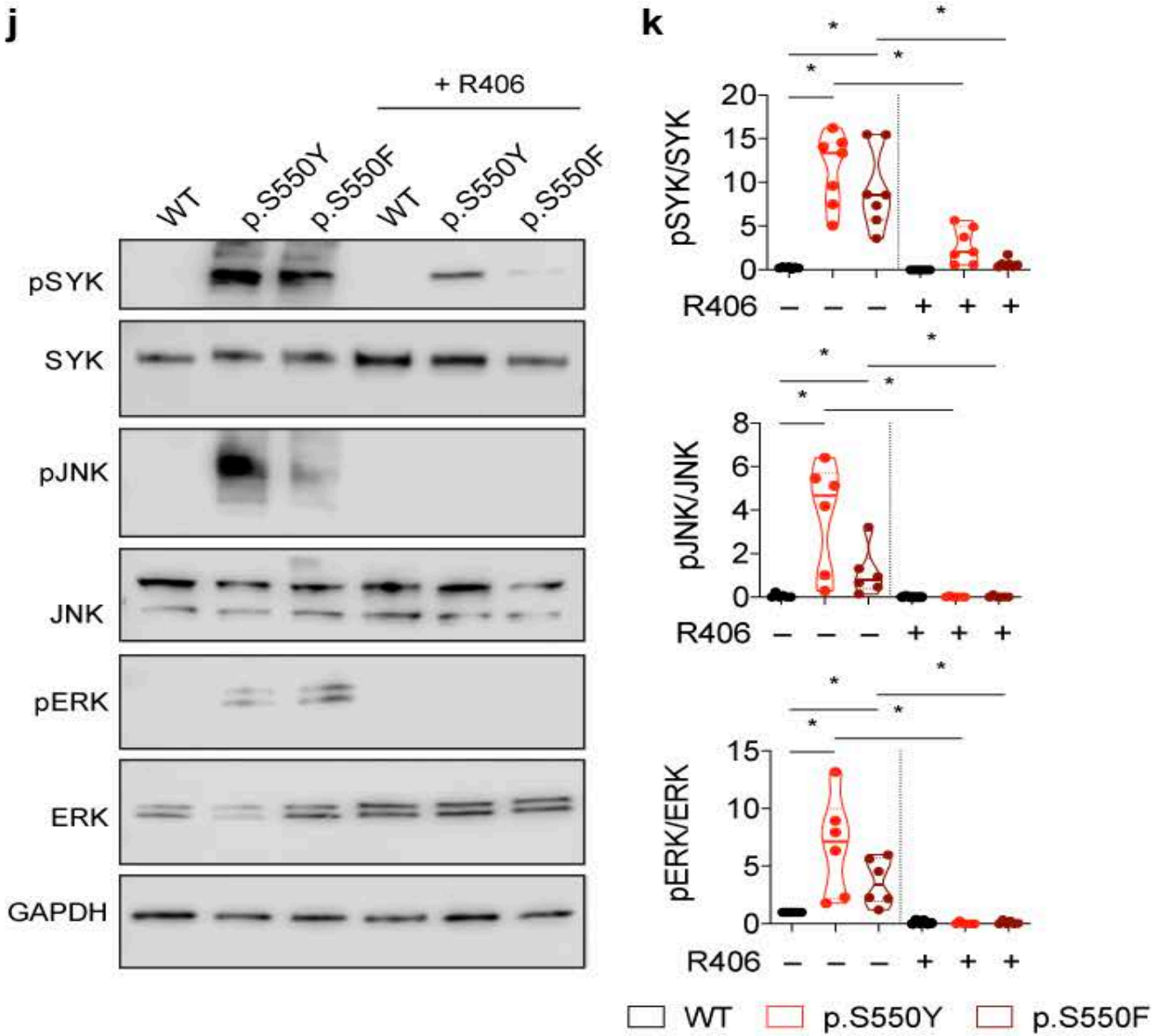
CRISPR-Cas9-mediated knockin mouse – Syk$^{S544Y(HZ)}$ – Osteoclast Activation -

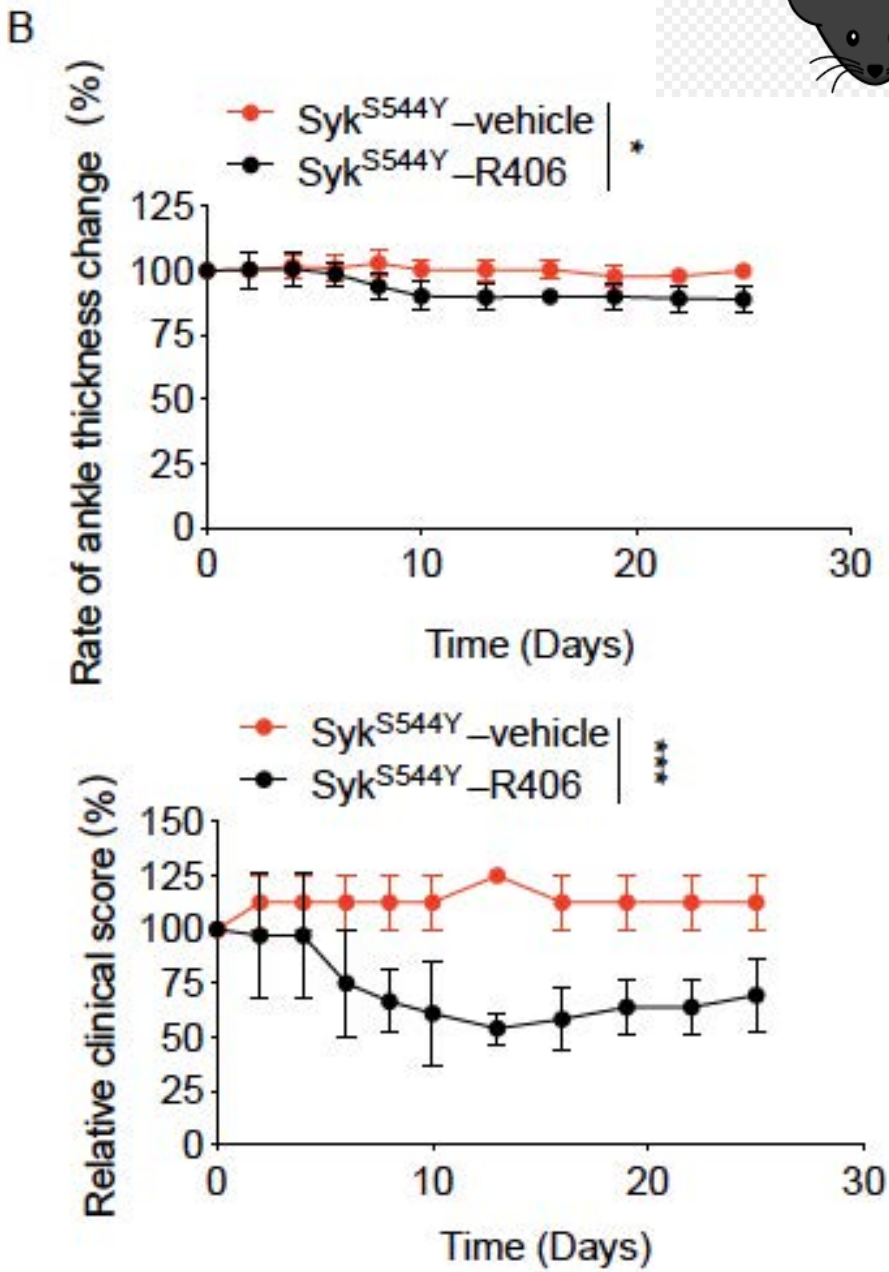


Fostamatinib (R406) Treatment
“small molecule Syk kinase inhibitor”



Fostamatinib Treatment





Transplant of Bone Marrow From Syk$^{S544Y(HZ)}$

Bone marrow transplantation

Mouse model:

Syk(S544Y) BMs → *WT mice*

WT BMs → *WT mice*

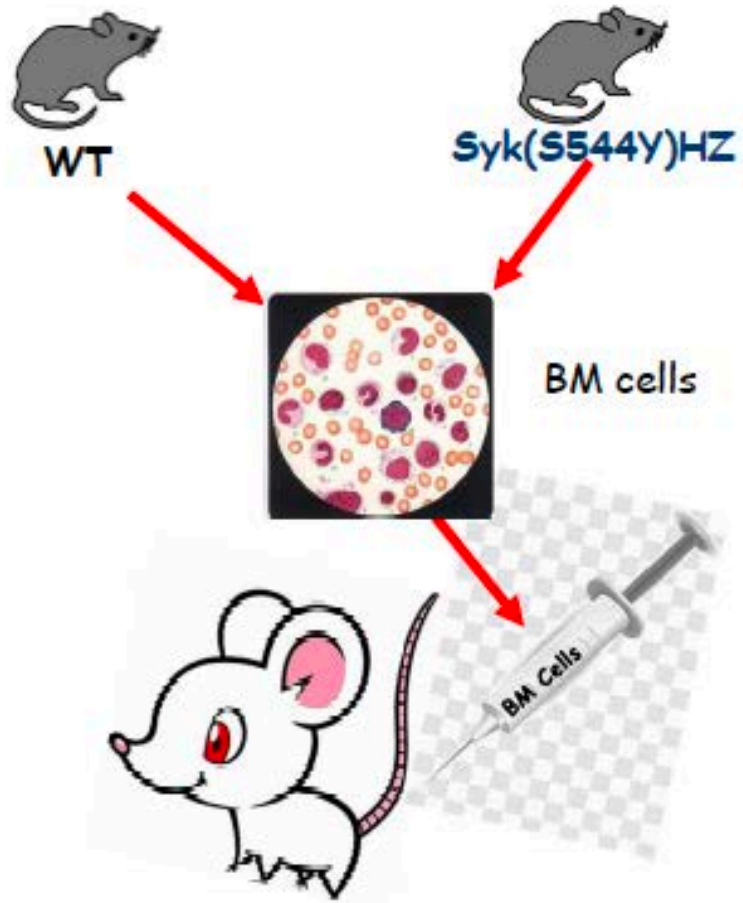
X-Ray 7.5Gy

day 0

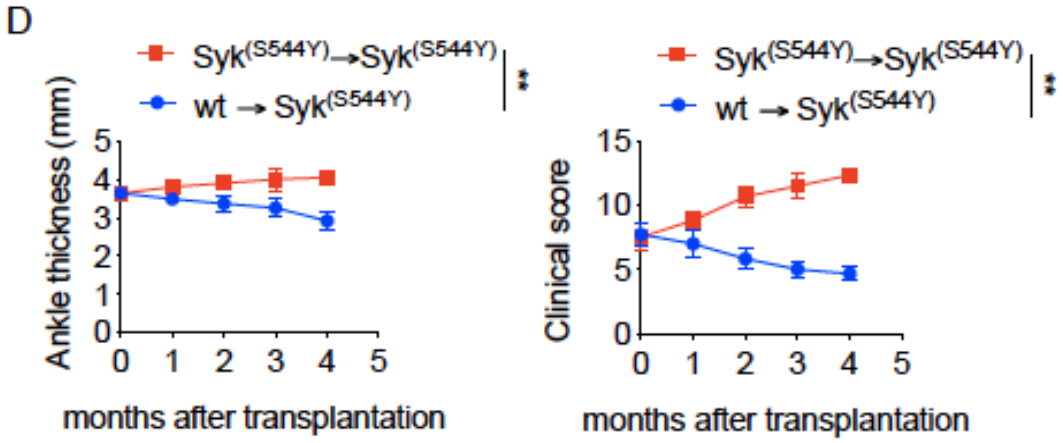
Time

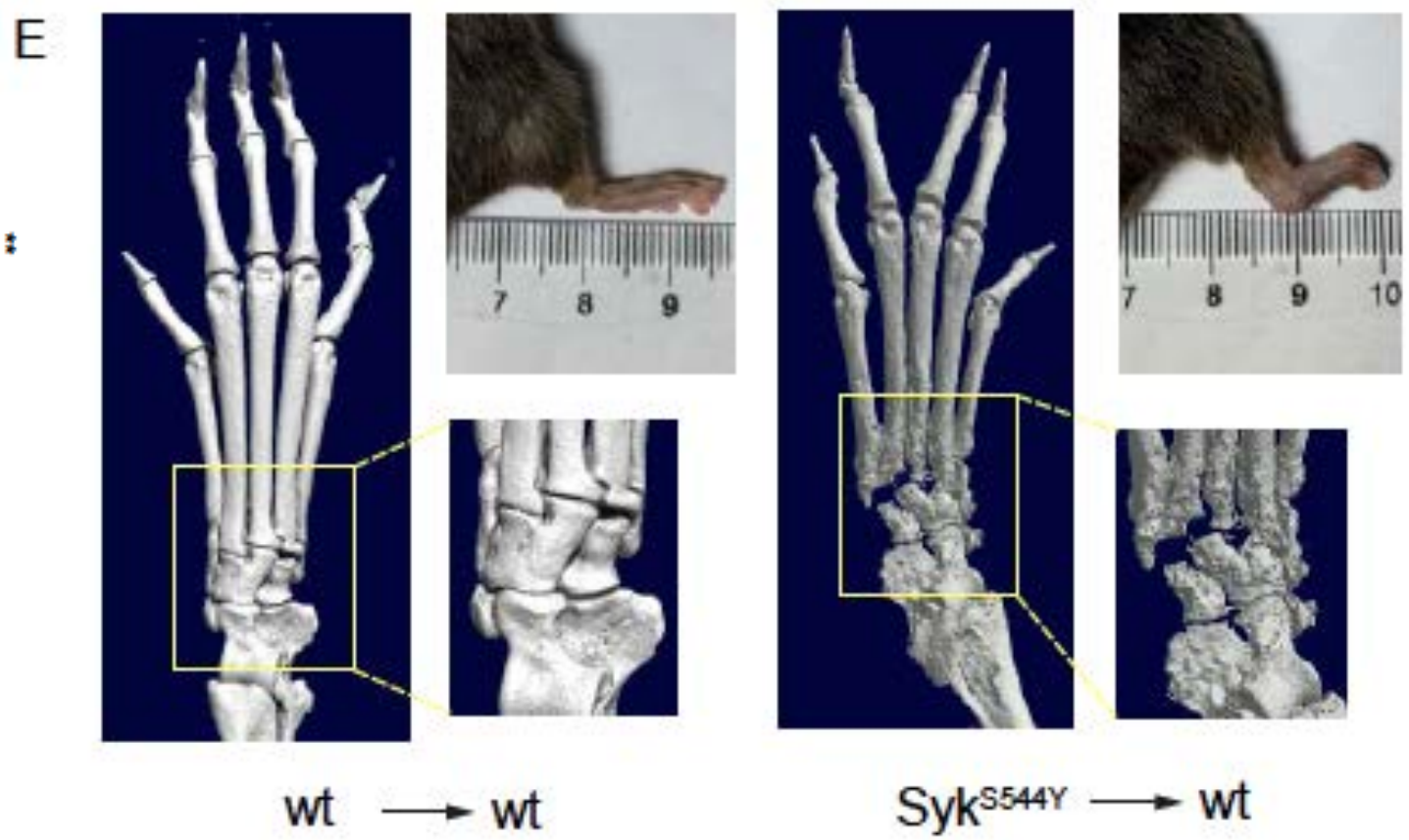
Sacrifice mice
5 months later

Transplant 3 million BM cells by tail vein

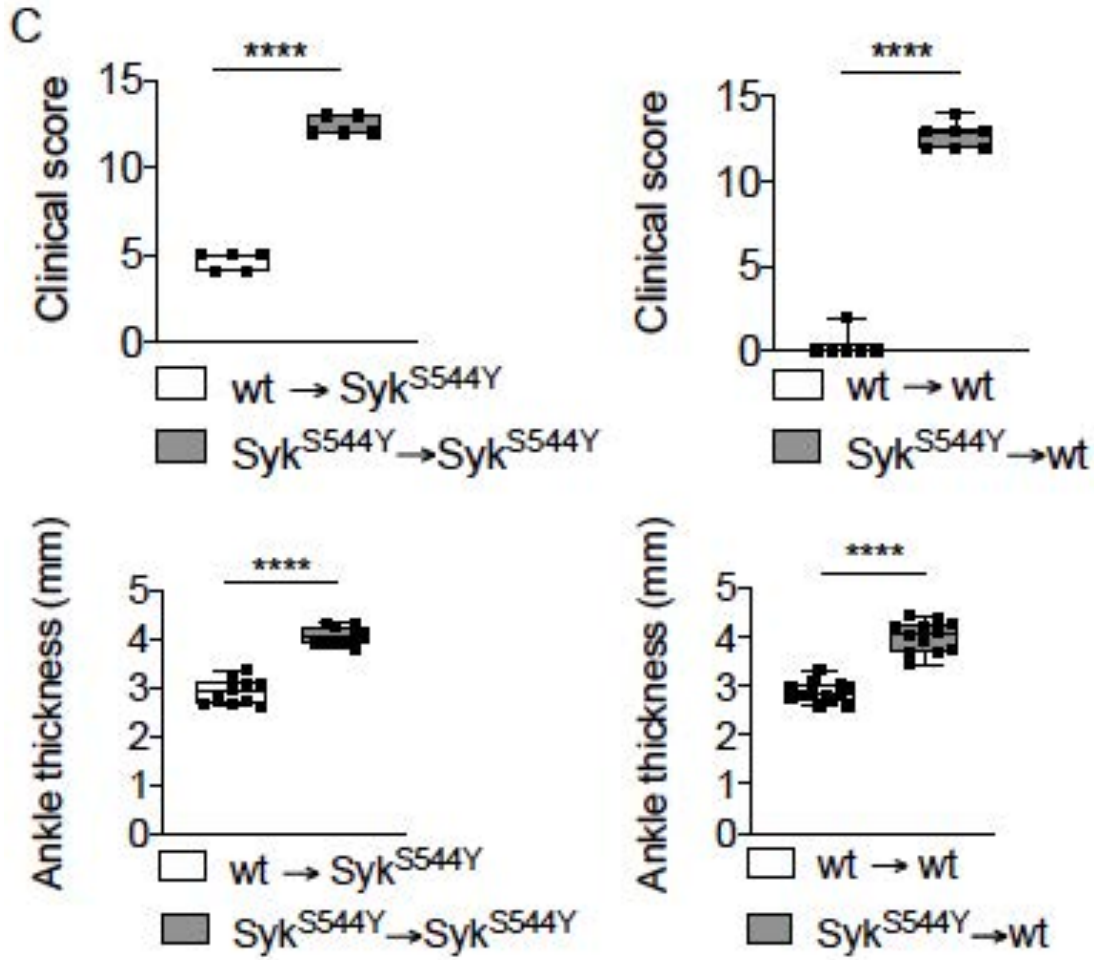


Disease Transferred by $Syk^{S544Y(HZ)}$ Bone Marrow





$Syk^{S544Y(HZ)}$ Mice “cured” by WT Bone Marrow



SickKids Patient 2
now 18 months of age
How to treat???

SYK – GOF – new autoinflammatory disorder

Hyperactivation of SYK

Systemic Inflammatory Disease and Immune Dysreguation

Immune Dysregulation – B-cells??

Colitis - ? Mechanism? CARD9 – fungal..?

Focus of ongoing studies – many……

Understanding role in VEOIBD

Druggable – small molecule inhibitors available

Patient 2 – **PRECISION TREATMENT** – Rituximab – CD20 B-cells – based on Patient 4 and Biology – Patient 2 and 3 “in remission”

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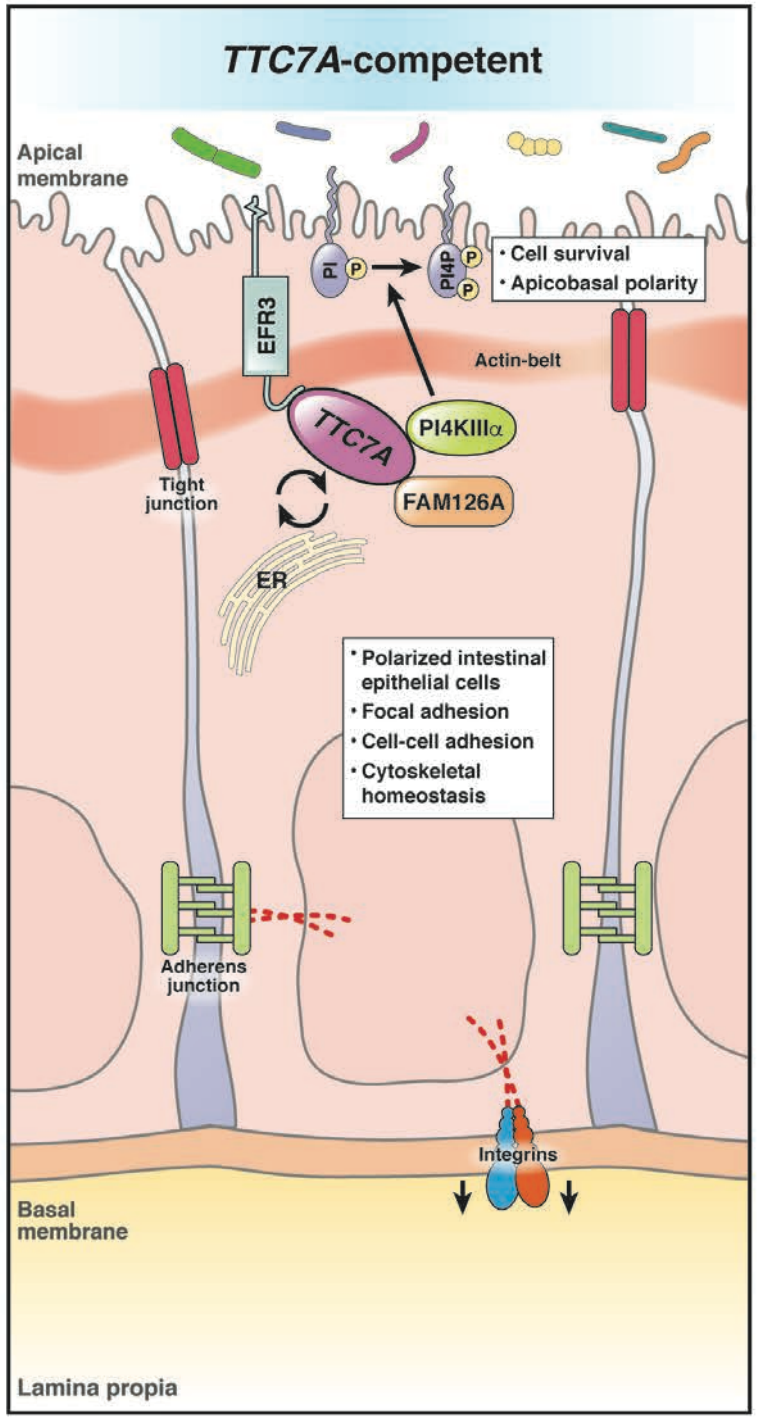
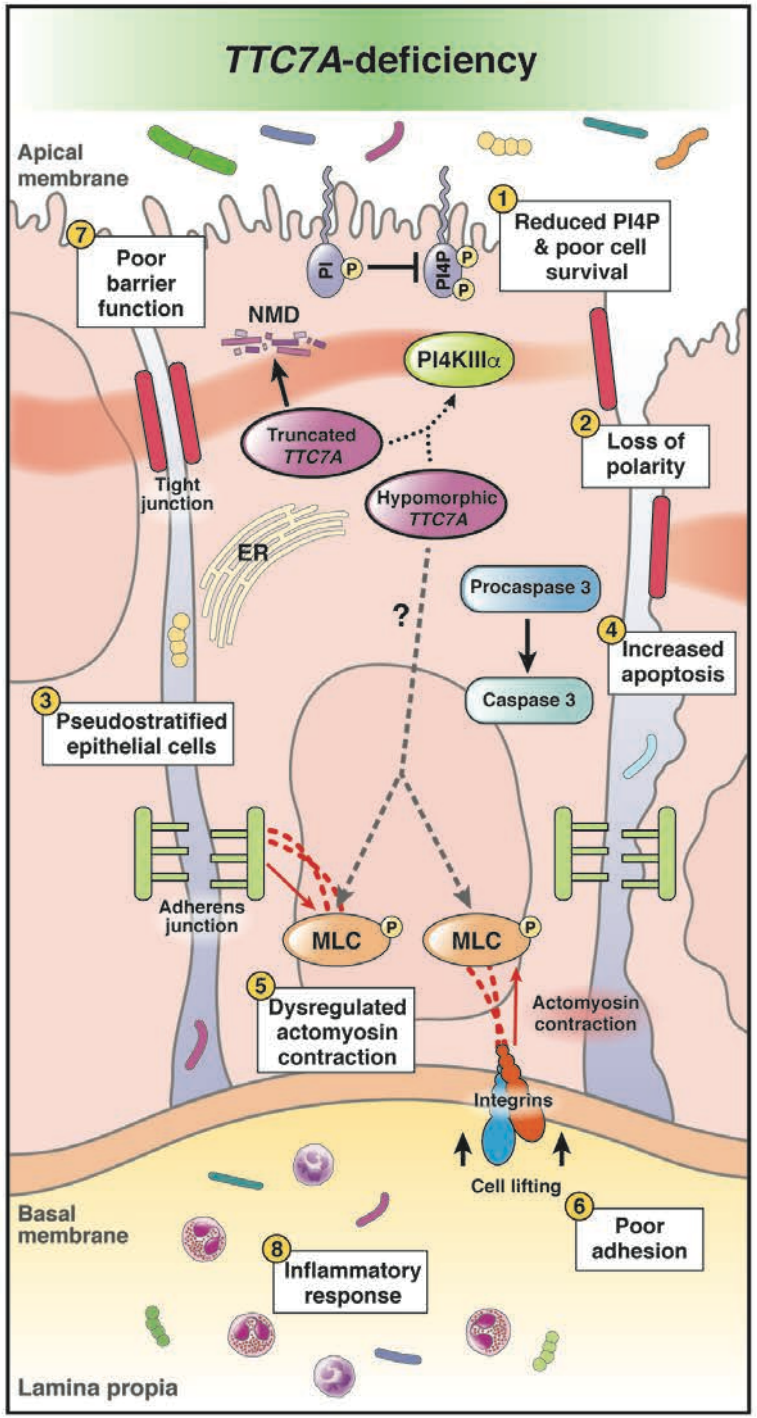
What can we learn from VEOIBD Genes?

Novel Treatments for severe IBD?

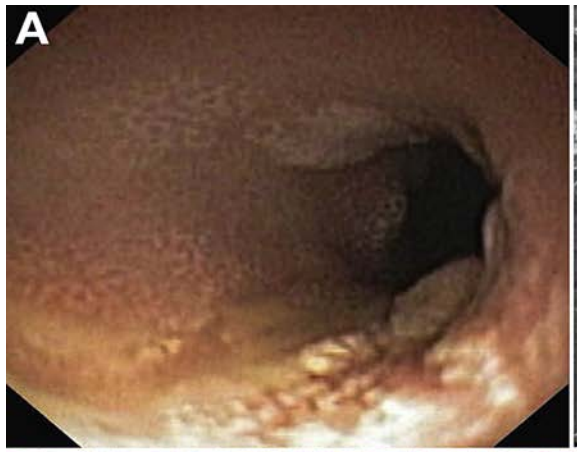
Mechanism of Disease

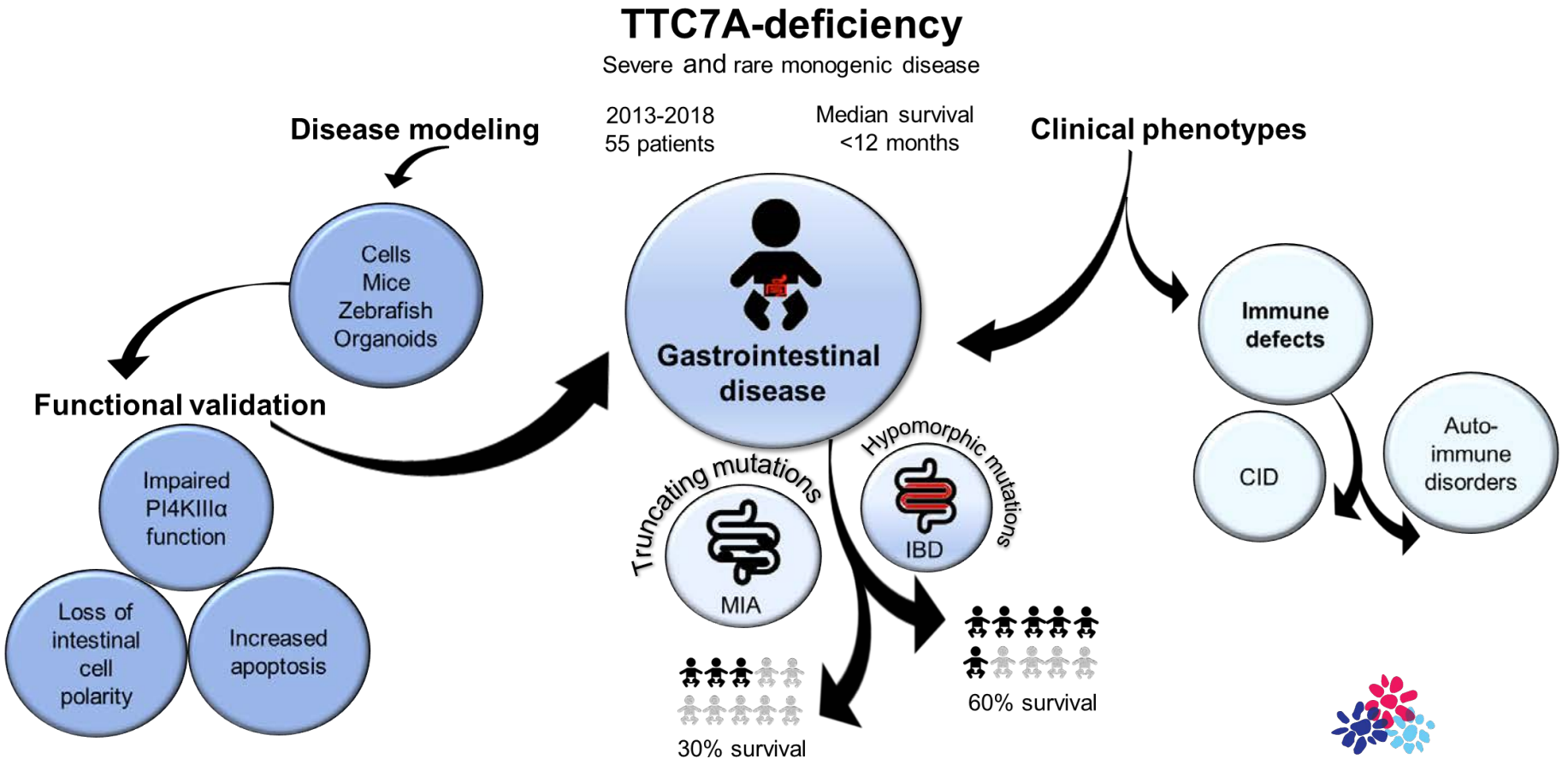
Jardine and Muise, CMGH 2019





Identified Rare Disease – 80% of Patients do not make it to their 2nd Birthday





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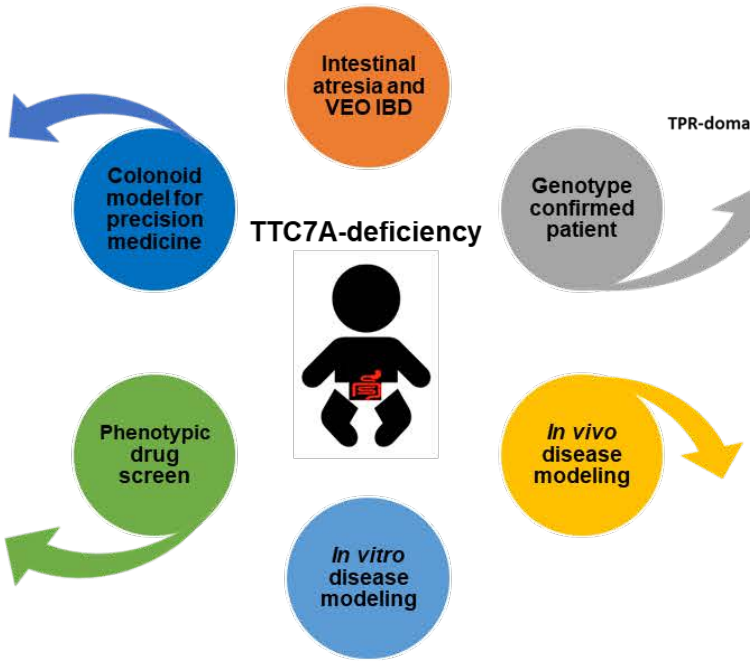


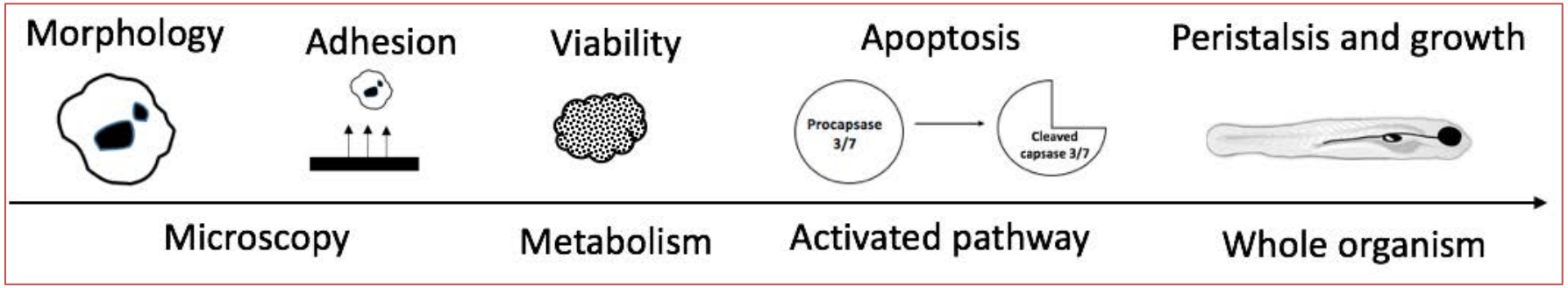
Miller Family – Seth and Eliza

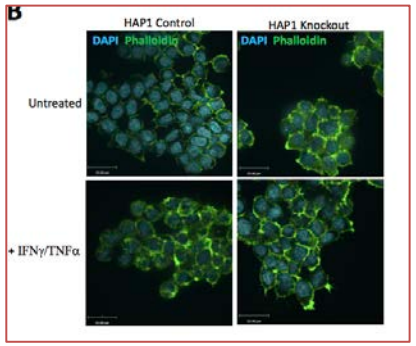
A repurposing drug screen identifies Leflunomide as a novel therapeutic for monogenic inflammatory bowel disease caused by TTC7A-deficiency

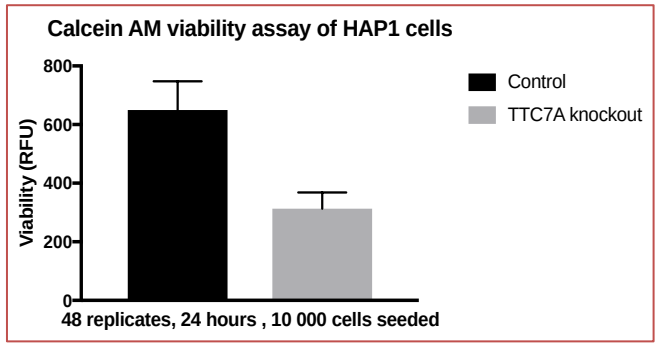
Gastroenterology 2020;158:1000–1015

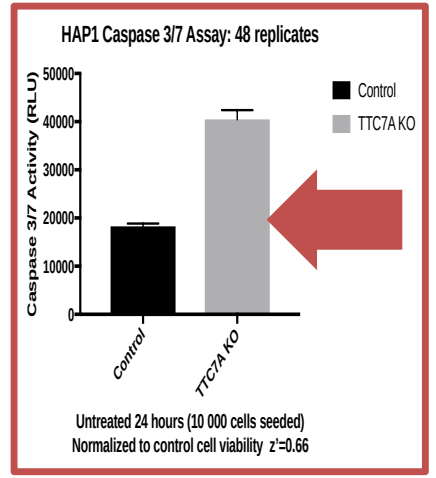
How to treat TTC7A–deficiency?
FDA-Approved Small Molecule Screen

Sasha Jardine



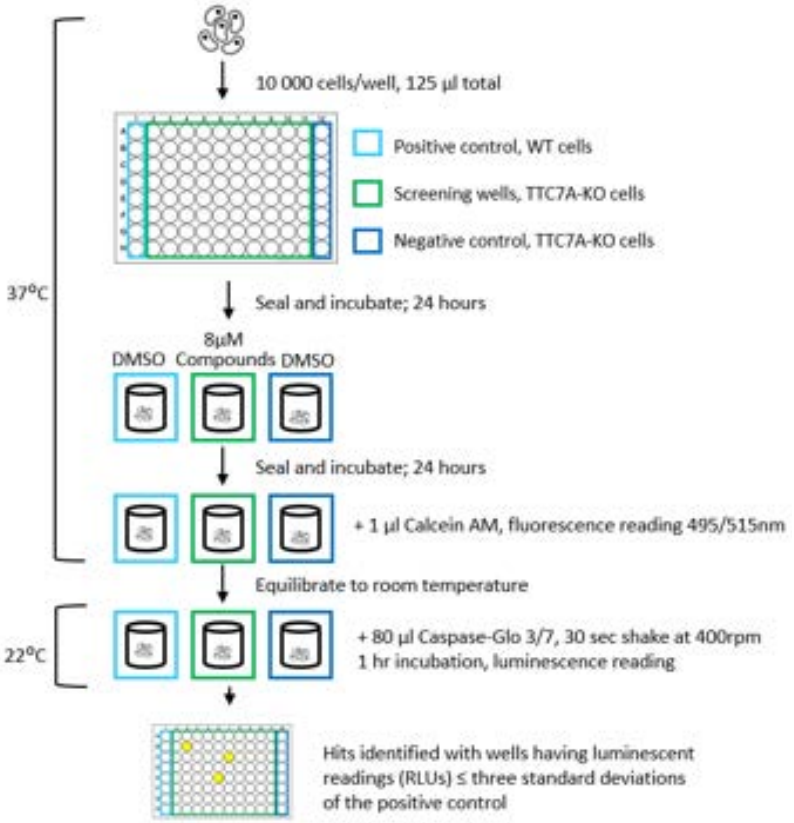


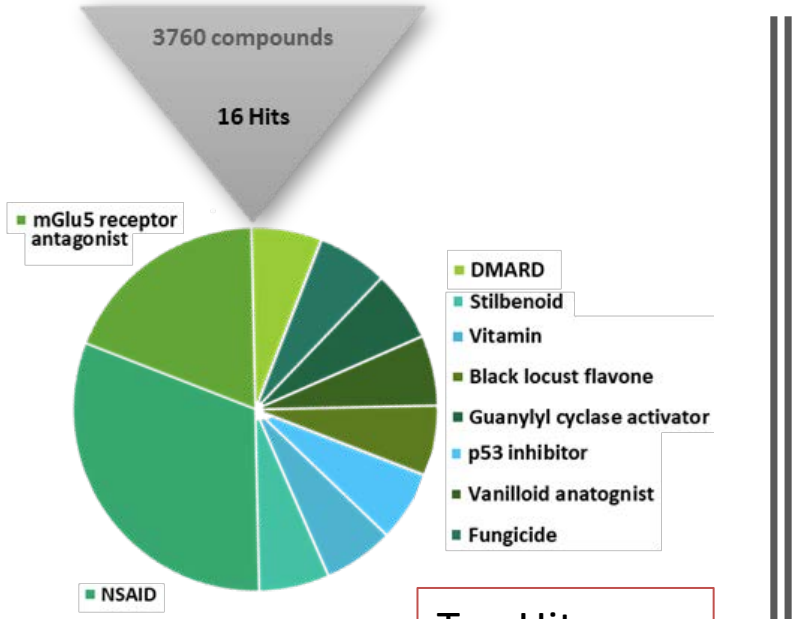




NEOPICS

Gastroenterology 2020;158:1000–1015





Top Hit – 96% rescue of apoptosis phenotype

Compound Name	Structure	Formula Structure	Molecular Weight (g/mol)	IC 50 (µm)	Decrease in caspase 3/7 activity	Compound description
Leflunomide***		C12H9F3N2O2	270.2	1.1	96%	Arava, immunosuppressive modifying anti rheumatic drug Disease Modifying Anti Rheumatic Drug (DMARD) - Pyrimidine synthesis inhibitor
Tiaprofenic acid		C14H12O3S	260.3	2.5	87%	NSAID, arthritic pain
Tiabendazole		C10H7N3S	201.3	11	60%	Fungicide, vascular disrupting agent
Cyanocobalamin		C63H88CoN14O14P	1355	11	64%	Synthetic form of B12
Flurbiprofen**		C15H13FO2	244.2	39	31%	NSAID, arthritis, increases P-Akt in rats (Sun B et al 2011)
Indoprofen		C17H15NO3	281.3	6.1	73%	NSAID, increase survival of motor neuron proteins, muscular atrophies. Withdrawn.
Fenbufen		C16H14O3	254.3	30	56%	Lederfen, NSAID, propionic acid derivatives class, withdrawn due to liver toxicity in 2010
Acacetin		C16H12O5	284.3	N/A	47%	Flavone from black locust used to treat arthritis. inhibition of recombinant human monoamine oxidases (MAO-A/B)
Resveratrol**		C14H12O3	228.3	4.9	45%	Prevents apoptosis in K562 cells by inhibiting lipoxygenase and cyclooxygenase activity
Isoliquiritigenin		C15H12O4	256.3	9.7	89%	Soluble guanylyl cyclase activator and aldose reductase inhibitor
SB-366791		C16H14N2O2Cl	287.7	7.6	58%	Vanilloid antagonist.Potent, selective, competitive vanilloid receptor-1 (VR1) antagonist.
SIB 1893		C14H13N	195.3	9.1	58%	Selective and noncompetitive antagonist of mGlu5 metabotropic glutamate receptor, positive allosteric modulator at mGluR
SIB 1757**		C12H11N3O	213.2	18	50%	Highly selective mGlu5 metabotropic glutamate receptor antagonist
Ketorolac tris salt		C15H12NO3• C4H12NO3	376.4	156	48%	Non-steroidal anti-inflammatory (NSAID) drug
MPEP hydrochloride**		C14H11N.HCl	229.7	6.3	33%	Glutamate antagonist. Highly selective, non-competitive mGluR5 (GCPR) metabotropic glutamate receptor antagonist.
Pifithrin-α hydrobromide		C16H18N2OS.HBr	367.3	8.3	31%	p53 inhibitor. Also aryl hydrocarbon receptor agonist

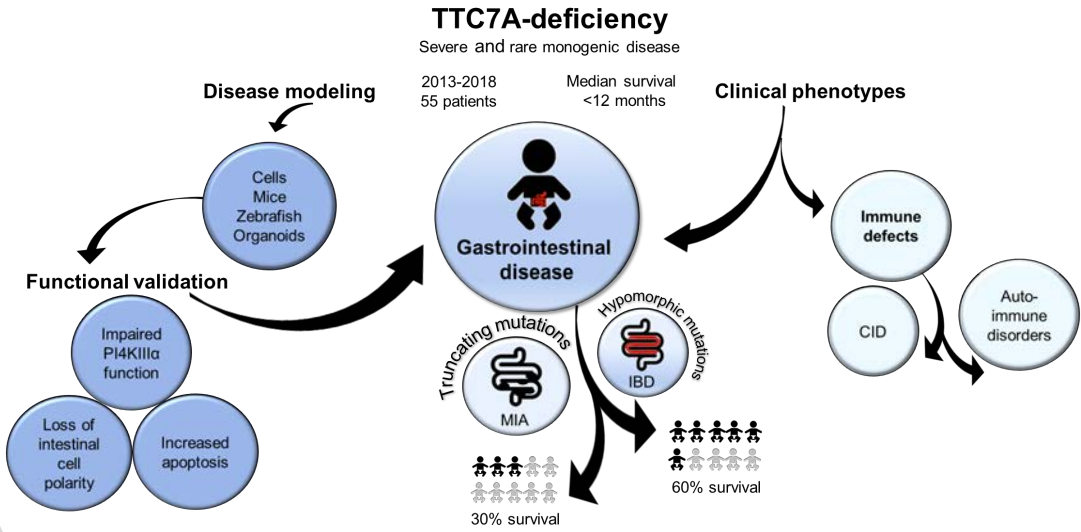
High-Throughput Drug Screen

3 libraries of FDA approved compounds/drugs (3760)
16 candidates from 10 drug classes

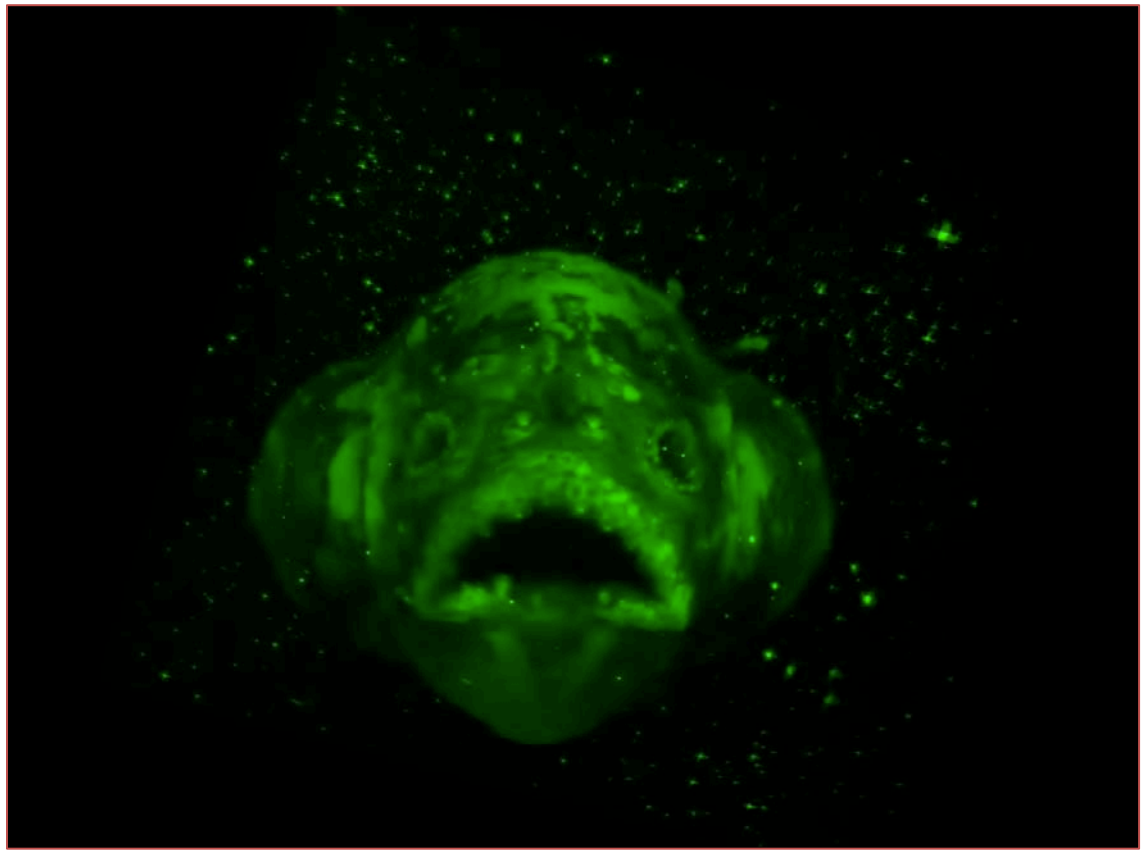
Lead Candidate - Leflunomide

- FDA-approved drug
- Use commonly in rheumatological disease
- Pediatric approved drug **(not really!)**
- Inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH) – required for DNA, RNA synthesis
- Off-patent – reduced $$
- Alternative mechanism of action
- Compassionate use possible

- Issues: route of administration – oral - severe intestinal disease, dosing……



Zebrafish: a model system to study intestinal disease



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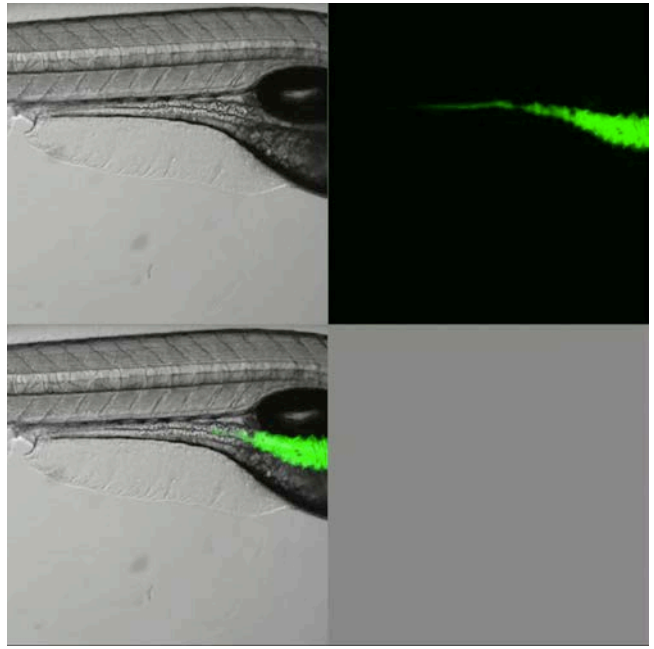
ttc7a -/- zebrafish Phenotype

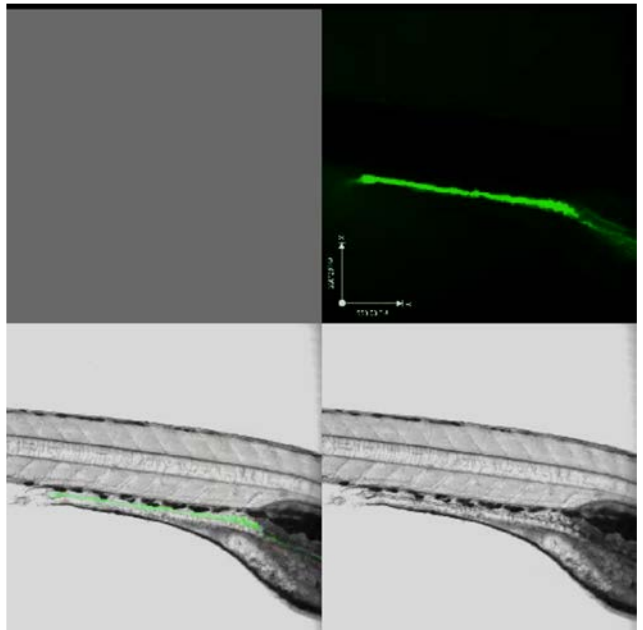
Peristalsis/Motility Assay

DCFH-DA

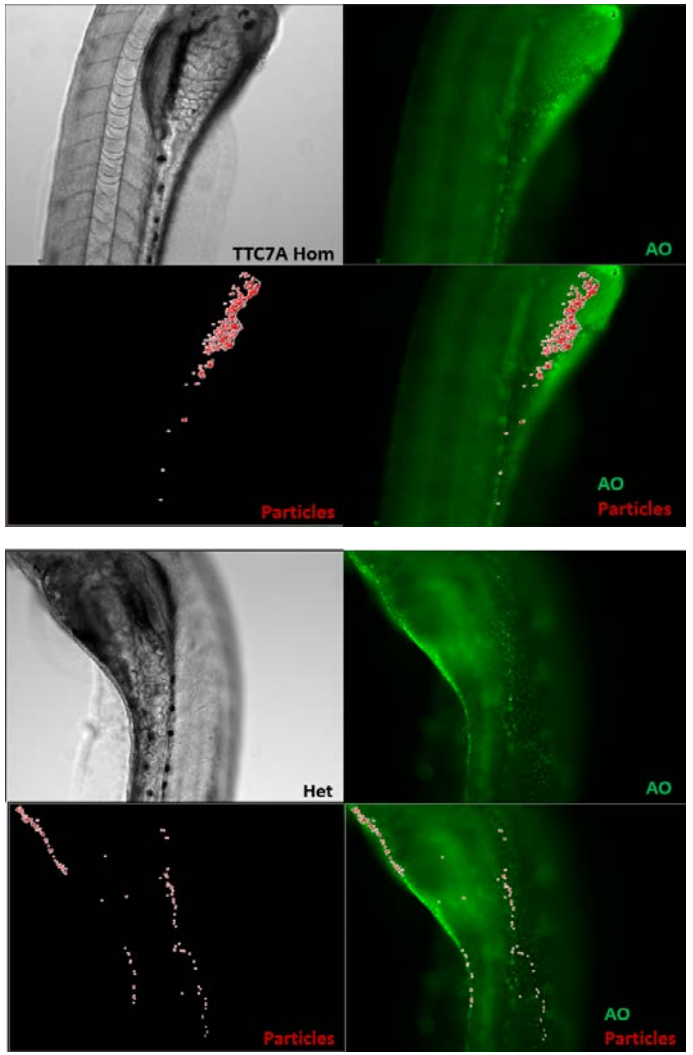
WT fish



Homozygous ttc7a fish



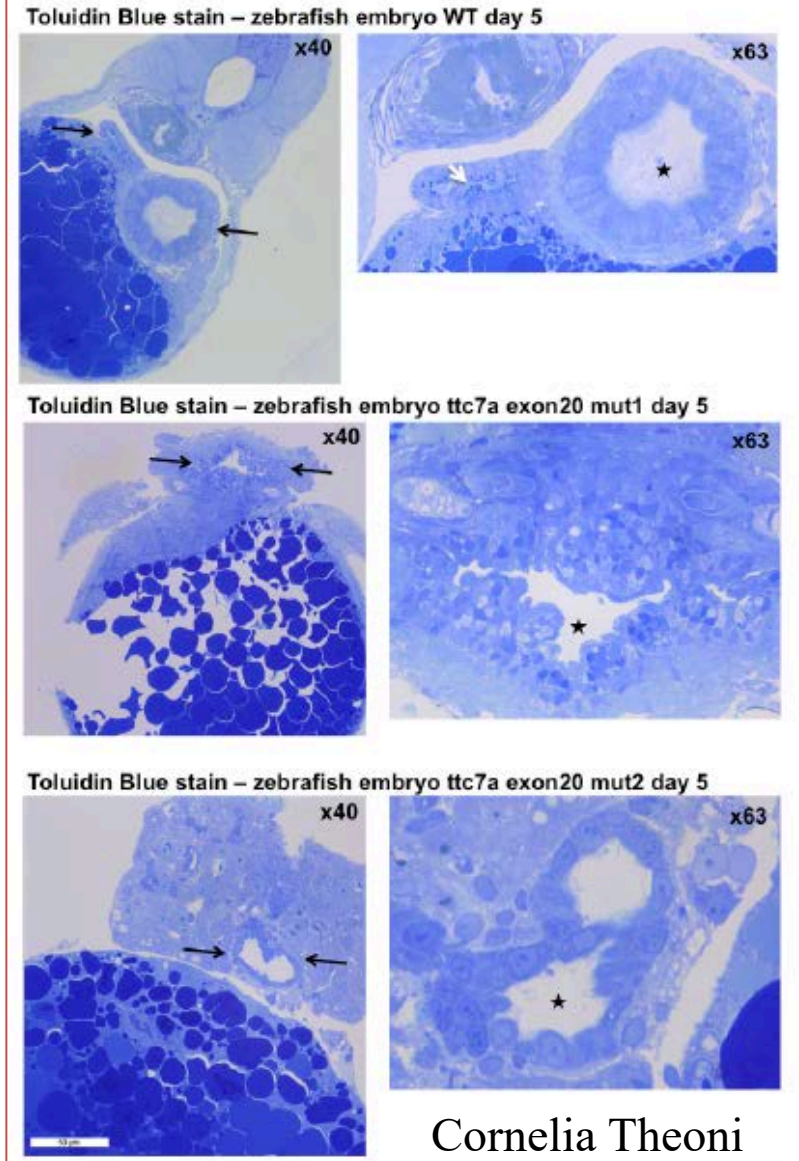
Apoptosis



acridine orange 10x

Sasha Jardine

Gut Pathology



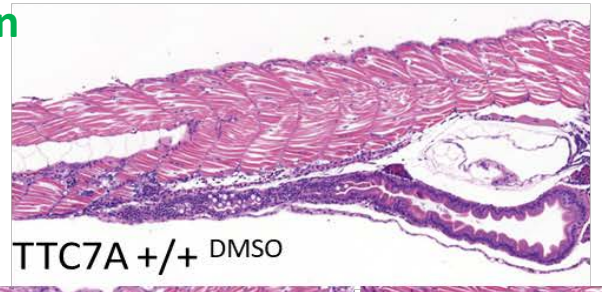
Cornelia Theoni

Gastroenterology 2020;158:1000–1015

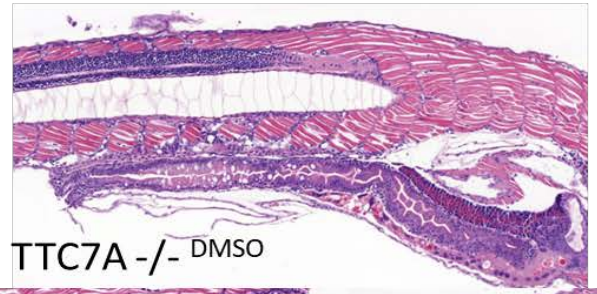
Drug treatment improves gut morphology *ttc7a* $^{-/-}$ zebrafish

Gastroenterology 2020;158:1000–1015

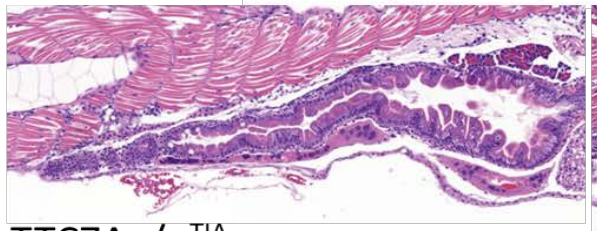
Intestinal lumen



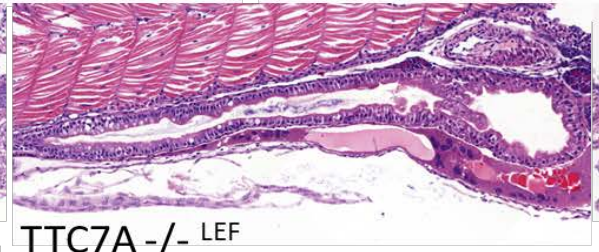
TTC7A +/+ DMSO



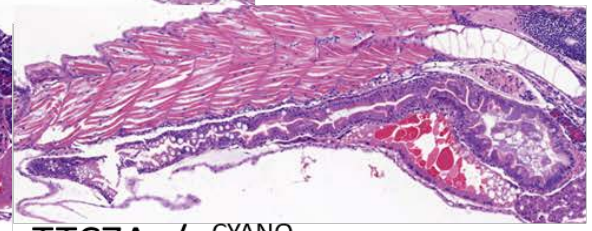
TTC7A -/- DMSO



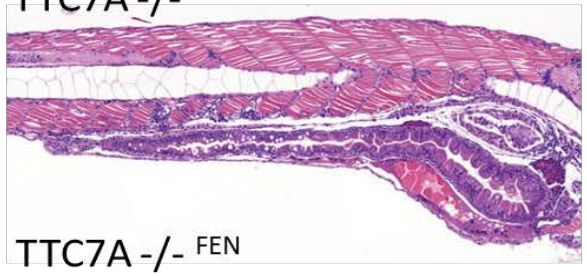
TTC7A -/- TIA



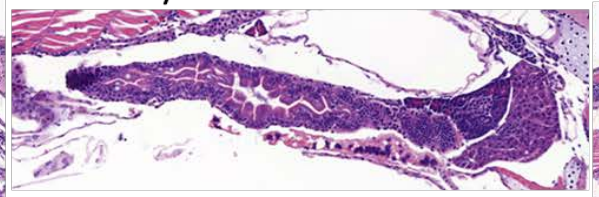
TTC7A -/- LEF



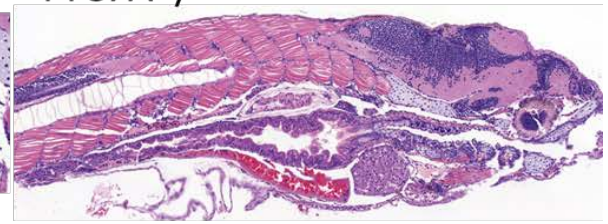
TTC7A -/- CYANO



TTC7A -/- FEN



TTC7A -/- FAS



TTC7A -/- 4-PBA

ROCK Inhibitor

- ✓ Open lumen
- ✓ Monolayer of simple columnar epithelial cells
- ✓ Discernible villi

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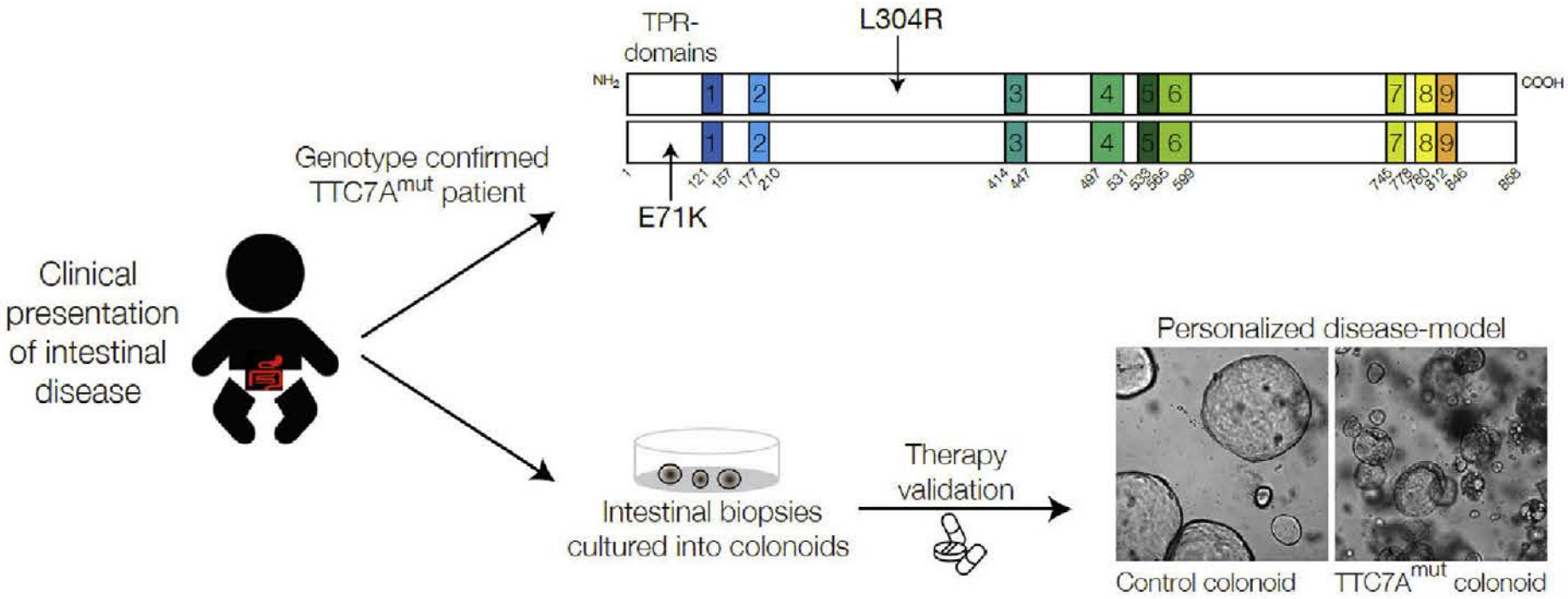
Human Organoids
Personalized Disease-Model

Rescue TTC7A–deficient Phenotypes (survival and function)

Jay Thiagarajah (BCH)



Gastroenterology 2020;158:1000–1015

Alternate Mechanism-of-Action pAKT

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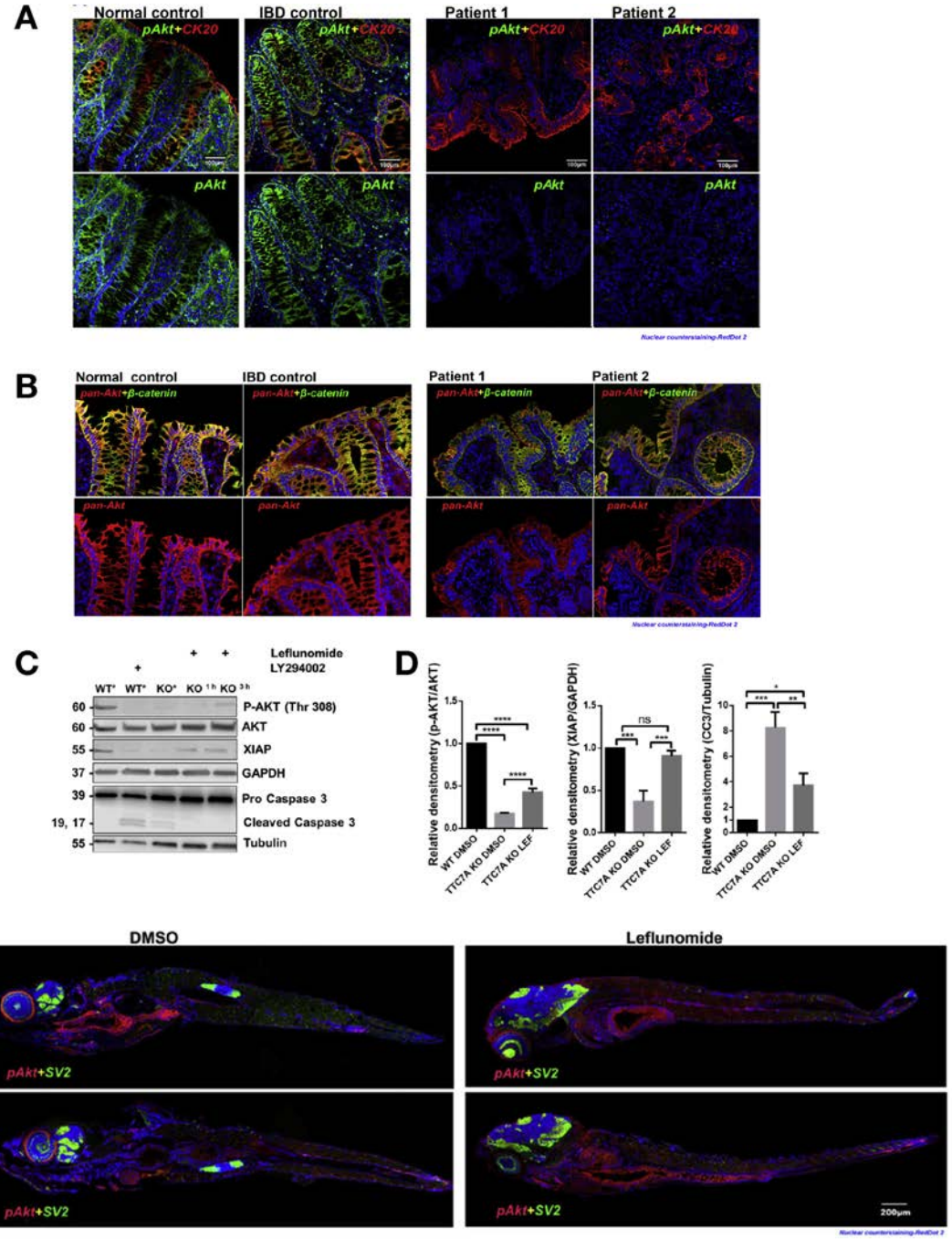
Gastroenterology 2020;158:1000–1015



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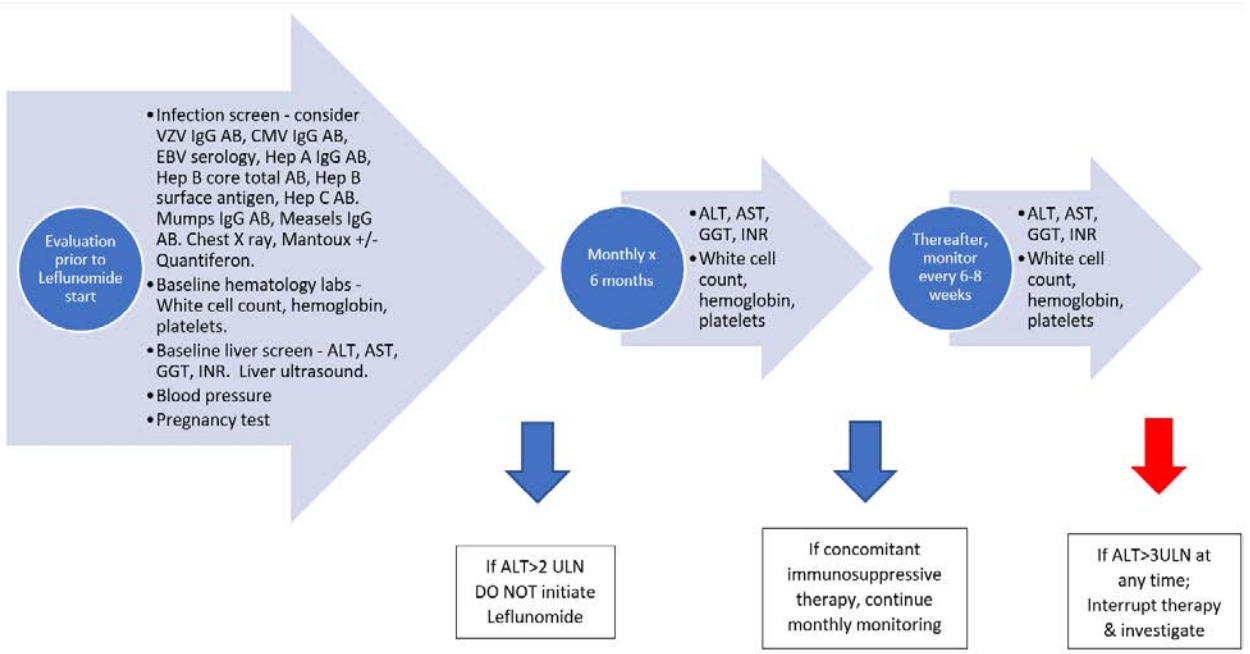
Series of N=1
Safety and Efficacy Trial



Aleixo.muise@utoronto.ca

Patient	Hospital	Responsible MD	Mutation	Type A. Stricturing B. Non-stricturing +/- PID	Age, presentation SSx, Pathology, Anatomy. Tubes Age of treatment	P T
1	Baylor, Texas	Karam, Lina Boujaoude lbkaram@bcm.edu; Kellermayer, Richard kellerma@bcm.edu	p.L478P p.A832V	B+	Infant: Male. Severe diarrhea, vomiting, Abdo pain, recurrent infections Immune: hypogammaglobulinemia and low NK cell number and function Intestinal: colitis Path: colon had eosinophilic infiltration with some areas of crypt loss/destruction, mild architectural distortion and mild, focal apoptosis Treated – 7 mos of age via Gtube Age of presentation: 13 days of life Age of starting Leflunomide: 7 mos (2/27/2020) Number of weeks on treatment: 26 weeks to date	T b a a
2	St. Justine, Montreal	Haddad Elie elie.haddad@umontreal.ca Marchand, Valerie valerie.marchand.hsj@ssss.gouv.qc.ca	p.G173D (paternal) c.1000_1001+2delAAGT (maternal) p.Q724K (paternal)	A+	Infant: -Meconium ileus and intestinal obstruction -Severe apoptotic colitis with dense eosinophilic infiltrations -Intravenous alimentation -Recurrence of intestinal obstructions -Multiple bowel stricture 4 years old: -Higher eosinophilic infiltration and high level of inflammation -Completely dependent of intravenous alimentation Immune deficiency with Lymphopenia, Monocytosis, Hypereosinophilia, Reduced memory B cell, Hypogammaglobulinemia Recurrent infections (lines sepsis, pneumonias, Pneumocystis jiroveci) Severe ichthyosis with hyperorthokeratosis on skin biopsy Age of starting Leflunomide: 5 years (January 2020)	T S P c p T t A D r C N D
3	BCH Boston, OLL Baton Rouge	Thiagarajah, Jay Jay.Thiagarajah@childrens.harvard.edu Elizabeth McDonough Elizabeth.McDonough@fmolhs.org	p.E71K p.L301R	B+	2yoF with pyloric web (resected), colitis (severe crypt architectural distortion, focal apoptosis), persistent upper and lower GI bleeding, vomiting, PN dependent for growth, immunodeficiency Age of presentation: 1 month Age of starting Leflunomide: 2.5 years Number of weeks on treatment: 20 weeks	P p b
4	GOSH, London, UK	Ed Gaynor Edward.Gaynor@gosh.nhs.uk	c.1204-3_1204-80 deletion	A+	laparotomy at 3 days of age which documented pyloric atresia, microcolon between the descending colon and the rectum with probable atretic sections, and areas of necrotic gut. CD8 and CD19 lymphopenia Ladd's procedure, a gastro-duodenostomy and an ileostomy formation	T S s

Series of N=1
Safety and Efficacy Trial

- **Safety:** No drug related adverse events including increase in LFTs (all 7 patients).

- **Efficacy (5 study patients):**
- 2 - infant patients with non-stricturing disease had improvement with resolution of clinical symptoms including diarrhea and vomiting, reduction in fecal calprotectin, and feeding improvement from TPN to enteral or G-tube feeds
- 1 – 12-month old patient with stricturing disease had reduction of strictures based on imaging (subsequently had BMT)
- 1 – five-year old patient with stricturing disease has not had any clinical improvement but is still on leflunomide treatment
- 1 - infant with stricturing disease “palliative” - started 1 month ago and showed improvement?

Funders:

Canada Research Chairs
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Instituts de recherche en santé du Canada

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NIH National Institute of Diabetes and Digestive and Kidney Diseases

Trainee Support:

Canadian Association of Gastroenterology
L'Association Canadienne de Gastroentérologie

Crohn's and Colitis Canada
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SickKids FOUNDATION

research training centre | Restracomp

Industry Partnership:

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Boston Children's Hospital Early Childhood IBD Initiative

Scott Snapper

Bruce Horwitz

Athos Bousvaros

Jeremy Goettel

Dror Shouval

Jodie Ouahed

Care-for-Rare FOUNDATION

Christoph Klein

Daniel Kotlarz

Dhaarini Mhurugan

Ehsan Bahrami

Jana Diestelhorst

Kaan Boztug

Max Witzel

Sibylle Koletzko

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Worldwide Contributing Sites >100 diagnosis so far

Country	Site	Participants
Australia	Children's Hospital Westmead	62
Australia	Sydney Children's Hospital Network	6
Brazil	Clinica Mon Petit Brazil	3
Brazil	Hospital Clinicas Unicamp	12
Brazil	Universite Federal Minas Gerais	2
Brussels	Cliniques Universitaires Saint-Luc	1
Canada	Alberta Children's Hospital	7
Canada	BC Children's Hospital	4
Canada	Centre Hospitalier Universitairede Sherbrooke	3
Canada	Children's Hospital of Eastern Ontario (CHEO)	68
Canada	CHU Sainte Justine	18
Canada	IWK Health Centre	8
Canada	Janeway Children's Hospital	3
Canada	Kelowna Gastroenterology Associates	1
Canada	Kingston General	2
Canada	London Health Science Centre	3
Canada	McMaster Children's Hospital	16
Canada	Montreal Children's Hospital/McGill	12
Canada	Stollery Childrens	79
Canada	Winnipeg Children's Hospital	24
Chile	Clinica Las Condes	3
Chile	Clinica Universidad de los Andes	3
Chile	Hospital Carlos VanBurn	3
Chile	Pontificia Universidad Católicade	40
China	Shenzhen Children's Hospital	14
Columbia	Hospital Pablo Tobón Uribe	3
Denmark	Odense Universitets Hospital	4
Germany	Ludwig Maximilians Universitat	2
Germany	Universitatsklinikum Ulm	3

Country	Site	Participants
Greece	Aghia Sophia Children's Hospital	14
Greece	Attikon University General Hospital	1
India	All India Institute of Medical Sciences Delhi	9
Ireland	Our Lady's Children's Hospital	116
Israel	Schneider Children's Medical Center	9
Israel	Shaare Zedek Medical Center	151
Italy	Istituto Giannina Gaslini	10
Japan	Gunma University Hospital	5
Mexico	Zambrano Hellion Tecnologico	3
Netherlands	Beatrix Children's Hospital	6
Netherlands	Erasmus University Medical Center	3
Netherlands	Utrecht	4
New Zealand	Starship Children's Health	15
Philippines	Philippines	3
Romania	University Medicine Pharmacy	3
Russia	St. Petersburg State Pediatric Medical University	1
Scotland	Royal Hospital For Sick Children Yorkhill	3
Spain	Corporacio Sanitaria Parc Tauli	3
Spain	Hospital Materno Infantil	21
Sweden	Umeå University	4
Turkey	Gazi University Medical School	3
Uruguay	Medica Uruguaya	9
USA	Albany Medical Center	3
USA	Baylor College of Medicine	3
USA	California Pacific Medical Center	2
USA	Children's Colorado	8
USA	Children's Hospital Boston	65
USA	Children's Hospital Los Angeles	9
USA	Children's Hospital Memorial Health	3

Country	Site	Participants
USA	Children's Hospital Oakland	3
USA	Children's Hospital Pittsburgh	45
USA	Children's Mercy Hospital	21
USA	Children's National Medical	17
USA	Connecticut Children's Medical Center	3
USA	GI Care For Kids	2
USA	Kapiolani Medical Center Hawaii	4
USA	Lurie Children's Hospital	5
USA	Memorial Healthcare System	3
USA	MUSC Children's Hospital	3
USA	Nationwide Children's Ohio	2
USA	Nemours/A.I. Dupont Children's Hospital	16
USA	Northwestern University	3
USA	Pediatric Gastroenterology Nutrition Associates	1
USA	Riley Hospital	3
USA	Santa Clara Medical Center	1
USA	Seattle Children's Washington	4
USA	Stanford University Medical Center	30
USA	Toledo Children's Hospital	3
USA	UCLA Medicine	9
USA	University Michigan	3
USA	University North Carolina Health Center	10
USA	University of Texas Houston	3
USA	University of Texas SouthWestern	3
USA	Vanderbilt University	8
USA	WNY Pediatric Gastroenterology	6
USA	Women & Children's Hospital	12
USA	Women & Infant's Hospital of Rhode Island	5
	ALL SITES TOTAL	1126

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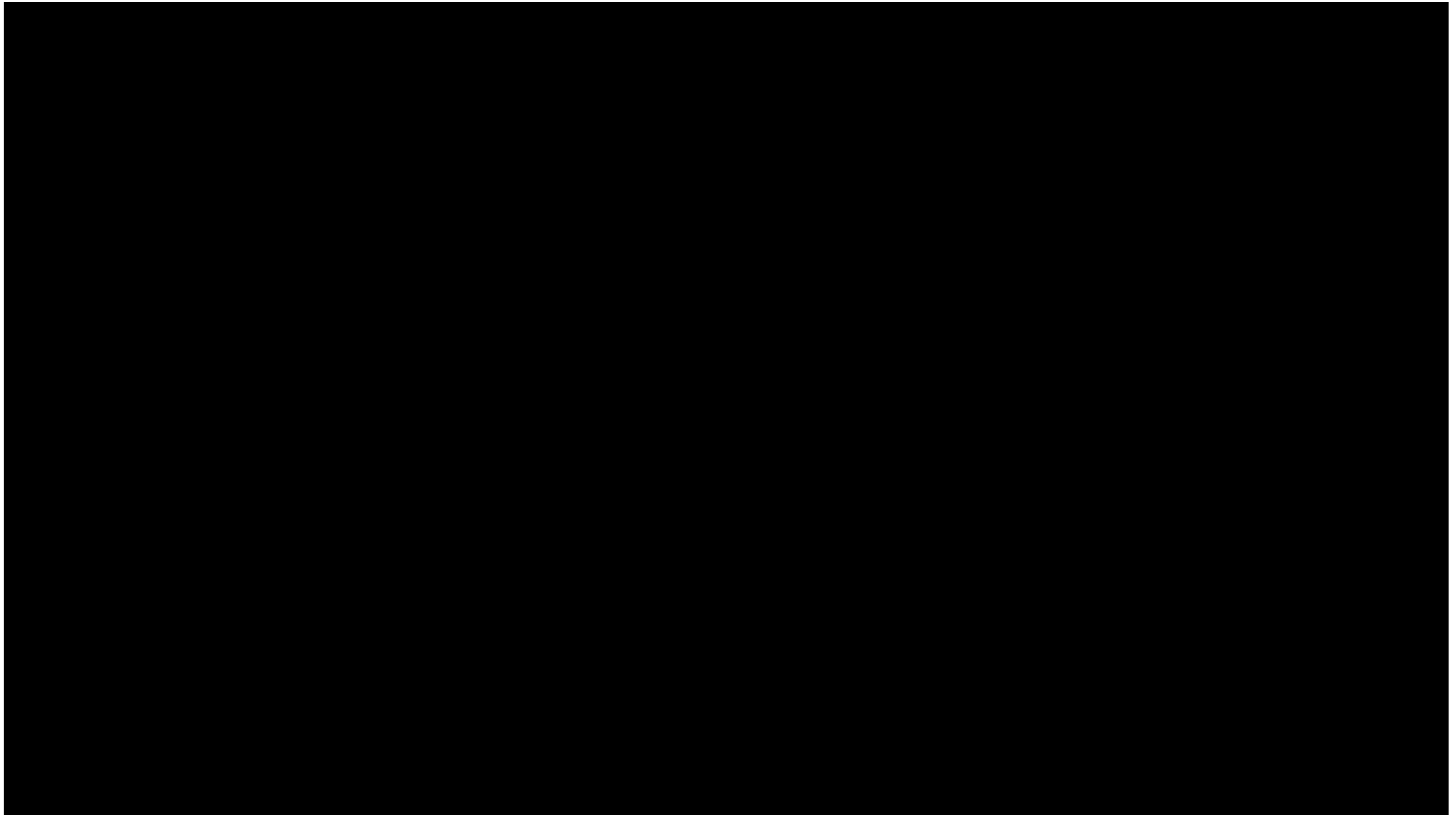

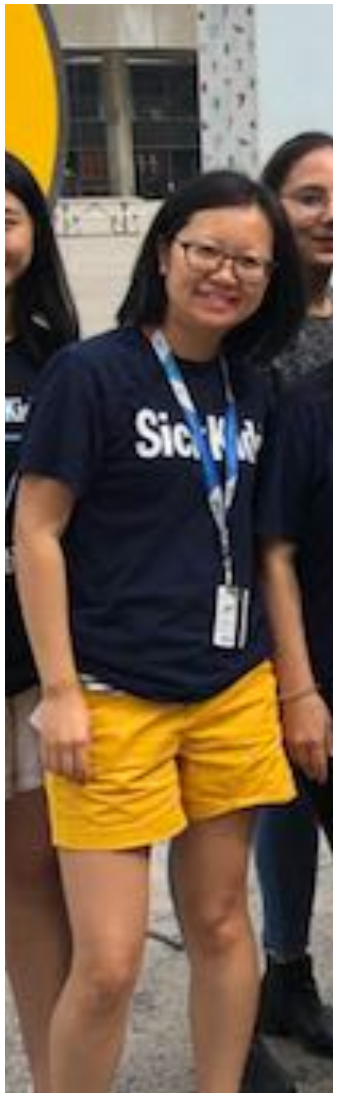

Cong-Hui Guo – Project Leader
Karoline Fiedler – NEOPICS Project Manager
Neil Warner, Jie Pan, Qi Li – Research Associate

Maggie Zhang
(Biobank and Sequencing)
Karen Frost- NP

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Acknowledgements – Muise Lab

Students, MDs, and PDF

- *Cornelia Thoeni
- *Lin Wang
- Gabriella Leung
- *Ramzi Fattouh
- *Abdul Elkadri
- Eileen Crowley
- * Takashi Ishige
- * Alessia Omenitti
- * Neda Moradin
- *Ziad Al Adham
- *Sandeep Dhillon
- *Neel Dhingani
- *Khalid Hossain
- Sasha Jardine
- Vritika Batura
- Zuhra Omary
- *Lucus Mastropaolo
- *Ryan Murchie
- Kelven Long
- Meera Mehta

- * Alumni

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Karoline Fiedler – NEOPICS Project Manager
Neil Warner, Jie Pan, Qi Li – Research Associate

Maggie Zhang, *Nancy Zhao, * Frozan Safi (Biobank and Sequencing)
Karen Frost- NP

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