RARE PATIENT ADVOCACY SYMPOSIUM

A partnership of
Penn Medicine Orphan Disease Center
and Global Genes

Global Genes®
Allies in Rare Disease

the orphan disease center

Sheraton University City Hotel

Saturday, May 19, 2018

7:00 am – 4:30 pm

How to Begin Research Collaborations

Hans Schlecht, M.D.

Physician, Baystate Health

Parent Advocate for SYNGAP

Mary Guilfoyle

Senior Director, Oncology Compound Team Leader

Janssen Pharmaceutical

RARE PATIENT ADVOCACY SYMPOSIUM

How to Begin Research Collaborations

Hans Schlecht, M.D.

Physician, Baystate Health

Parent Advocate for SYNGAP

How to Begin Research Collaborations

Hans P. Schlecht, MD, MMSc

hans.schlechtmd@baystatehealth.org

No conflicts of interest

RARE PATIENT ADVOCACY SYMPOSIUM

What I Hope to Cover

- Intro on my family's story
  - My background
  - March 2017
- The importance of communication
- Approach to cutting edge care
- Strategies
- Resources
- Options
- March 2017 to now

My background

- MD from New Jersey Medical School
- Internal Medicine and Infectious Diseases training at Beth Israel Deaconess of Harvard Medical School
- Completed a 2 year Clinical Investigator Training Program with a Masters Degree in Medical Sciences from MIT/HMS
- I have had funding from the NIH and Gates Foundation
- I actively think about translational and clinical research

Erich's WES, March 2017

SUMMARY OF FINDINGS

Results Related to Clinical Indication:

Gene	Variant
SYNGAP1	c.1507C>T; p.Q503*

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The Key is Communication

- The topic of the conversation:
  - You
  - Your disease
  - The research
  - Similar disease and its research
- Who to converse with:
  - Your doctor
  - The researchers
  - The advocates
  - Anyone!
- Where to converse

Bring your story everywhere

Palm Springs, CA

Payton Durrett – Birthdate 12-10-2007

Parents Andrea Durrett & Rocky Durrett

The Durrett Family - Finding the Normal Button

Around age 2, we knew something was going on with our little Payton. She wasn't talking as much as her sister. We always called her our quiet child. It took her almost 17 months to walk. During this time, we started looking into tests and procedures to uncover what's going on with Payton. We started with the pediatric doctor and neurologist, genetics and metabolic. Around age two and a half, maybe 3, an EEG revealed she was having seizures. Which broke our hearts? Many more tests were done all of which uncovered nothing. Until October 2014 (age 6). When we got a call from metabolic indicating they found what Payton has, Syngap1! What is that I asked? I was told it's a genetic mutation that causes for intellectual disability, apraxia of speech and seizures. Wow! No cure as of today, but maybe, there will be one day. This was hard to hear, but in the same breath, we had a label; an answer as to what is going on with Payton. How does this affect her? She is slower than most children her age. She has apraxia of speech, so she doesn't talk smooth like everyone else. She has to stop and think about what she wants to say. Payton is like a drunken sailor. She is off balance either due to her medication or her condition. She has low muscle tone and has many accidents and falls from time to time. She works hard to fit in and wants to be accepted. She is loved by many and her smile lights up the room. She is amazing with her determination to try hard and stubbornness to be independent.

We have tried cheerleading, but couldn't keep up with the routine. Swimming, but wasn't accepted on the swim team. Softball, which we never got to hit the ball and get on 1st base. Tried Soccer, but didn't like to be bossed around by her team mates. Currently, in Gymnastics and enjoying it. She loves to create and color and paint. She might be an artist at heart. We love her for everything she does and is and wouldn't change anything other than this genetic mutation. If we could give her anything in life, it would be to have all the abilities that the rest of us have. The ability not to allow seizures to intrude on her capacity to learn and grow. The power to increase her intelligence and grow up and have a career and a family and to be loved and appreciated and give back to the world in a way that she would enjoy. I pray that continued research finds solutions to help us find the normal button. Thank you for reading our story and for not giving up for our family and many others...

Thank you for all your help with my 9 year old - All my best Andrea Durrett

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Temple City, CA, 91780
(p) 626-350-0537 (f) 626-454-1667
info@fulgentdiagnostics.com
www.fulgentdiagnostics.com

fulgent diagnostics

CLIA ID: 05D2043189
Laboratory Director:
Dr. Hanlin (Harry) Gao, PhD FACMG

Report Date: 09/23/14

Patient
Name: **Durrett, Payton**
DOB: 12/10/2007
Gender: F
MR#: 3360090

Acc#: 1401716
Specimen type: Blood
Draw date: 00/00/00
Received Date: 08/28/14
Authorized Date: 08/28/14

Physician: Richard Chang
Children's Hospital of Orange
1201 W. LaVeta Ave
Orange CA 92868
Phone: 714-509-4741
Fax: 714-509-8362

TEST PERFORMED: CLINICAL EXOME NGS PANEL – 4635 GENES

RESULT: **2 PATHOGENIC VARIANTS AND 1 LIKELY PATHOGENIC VARIANT DETECTED**

GENE	VARIANT	ZYGOSITY	INHERITANCE	CLASSIFICATION
SYNGAP1 NM_006772.2	c.333del p.Lys114Serfs*20	Heterozygous	Autosomal Dominant	Pathogenic
FTCD NM_006657.2	c.990dup p.Pro331Alafs*2	Heterozygous	Autosomal Recessive	Pathogenic
MYO7A NM_000260.3	c.4450C>T p.Leu1484Phe	Heterozygous	Autosomal Recessive	Likely Pathogenic

INTERPRETATION:

A Heterozygous change, NM_006772.2:c.333del (p.Lys114Serfs*20) in Exon: 04 of the SYNGAP1 gene was identified in the submitted specimen (OMIM ID: 603384). Mutations in this gene can cause autosomal dominant mental retardation. This variant is predicted to cause a frameshift, which alters the protein's amino acid at codon 114 and leads to a premature stop codon 20 position downstream. This alteration is then predicted to lead to a truncated protein and loss of function. This variant is classified as a Pathogenic variant based on ACMG guidelines.

A Heterozygous change, NM_006657.2:c.990dup (p.Pro331Alafs*2) in Exon: 09 of the FTCD gene was also identified in the submitted specimen (OMIM ID: 606806). Bi-allelic mutations in this gene can cause an autosomal recessive glutamate formiminotransferase deficiency, which is characterized by elevated levels of formiminoglutamate in the urine in response to histidine administration, megaloblastic anemia, and mental retardation, developmental delay. This variant has been previously reported in a patient with Glutamate formiminotransferase deficiency (PubMed: 12815595). This alteration results in a premature stop codon at amino acid position 331 and leads to a truncated protein, so it is classified as a Pathogenic variant based on ACMG guidelines. A second mutation in this gene was not detected, however, the presence of large deletions or duplications or mutations in other regulatory regions cannot be ruled out. The clinical significance of heterozygous of mutation/variant in this gene is unknown.

A Heterozygous change, NM_000260.3:c.4450C>T (p.Leu1484Phe) in Exon: 34 of the MYO7A gene was also identified in the submitted specimen (OMIM ID: 276903). This variant has been previously reported in a patient with Usher syndrome 1 (PubMed: 16470552). The allele frequency for this variant is 0.0% in the dbSNP database and 0.04% (3/8342) in European Americans and 0.02% (3/12418) in the overall population in the NHLBI exome sequencing project, indicating it is not a common benign variant. Computational Tools: (Align GVGD = likely benign (C15), SIFT = Deleterious, MutationTaster = disease causing, MAPP = bad and Polyphen2 = probably damaging). The physiochemical difference between Leu and Phe is small (Grantham dist.:22 [0-215]). This variant is located in the FERM domain. Amino acid Leu1484 is highly conserved in evolutionarily distant

Patient: Durrett, Payton, Accession number: 1401716, Test: Clinical Exome NGS Panel – 4635 genes

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Up your knowledge base

- Disease- do the best you can
- Research
  - Epidemiology, basic science, clinical research…
  - Clinical Trials
- Similar diseases
  - Ras-opathies and Infantile encephalopathies
  - Leslie Gordon, MD PhD and the Progeria Research Foundation and their approach

RARE PATIENT ADVOCACY SYMPOSIUM

Disease(+) information

- Google and set Scholar Alerts
- Youtube
- Foundations
- NIH
- GARD
- Pubmed
- FDA
- …

Pubmed

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US National Library of Medicine
National Institutes of Health

PubMed Search
Advanced Help

Format: Abstract Send to

Mol Cell Neurosci. 2018 Mar 24. pii: S1044-7431(18)30030-7. doi: 10.1016/j.mcn.2018.03.008. [Epub ahead of print]

Species-conserved SYNGAP1 phenotypes associated with neurodevelopmental disorders.

Kilinc M[1], Creson T[2], Rojas C[2], Aceti M[2], Ellegood J[3], Vaissiere T[2], Lerch JP[4], Rumbaugh G[5].

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4 Mouse Imaging Centre, Hospital for Sick Children, Toronto, ONT, Canada; Medical Biophysics, University of Toronto, Toronto, ONT, Canada.
5 Graduate School of Chemical and Biological Sciences, The Scripps Research Institute, Jupiter, FL, United States; Department of Neuroscience, The Scripps Research Institute, Jupiter, FL, United States. Electronic address: grumbaug@scripps.edu.

Abstract

SYNGAP1 loss-of-function variants are causally associated with intellectual disability, severe epilepsy, autism spectrum disorder and schizophrenia. While there are hundreds of genetic risk factors for neurodevelopmental disorders (NDDs), this gene is somewhat unique because of the frequency and penetrance of loss-of-function variants found in patients combined with the range of brain disorders associated with SYNGAP1 pathogenicity. These clinical findings indicate that SYNGAP1 regulates fundamental neurodevelopmental processes that are necessary for brain development. Here, we describe four phenotypic domains that are controlled by Syngap1 expression across vertebrate species. Two domains, the maturation of cognitive functions and maintenance of excitatory-inhibitory balance, are defined exclusively through a review of the current literature. Two additional domains are defined by integrating the current literature with new data indicating that SYNGAP1/Syngap1 regulates innate survival behaviors and brain structure. These four phenotypic domains are commonly disrupted in NDDs, suggesting that a deeper understanding of developmental Syngap1 functions will be generalizable to other NDDs of known or unknown etiology. Therefore, we discuss the known molecular and cellular functions of Syngap1 and consider how these functions may contribute to the emergence of disease-relevant phenotypes. Finally, we identify major unexplored areas of Syngap1 neurobiology and discuss how a deeper understanding of this gene may uncover general principles of NDD pathobiology.

KEYWORDS: Autism spectrum disorder; Circuits; Cognitive impairment; Epilepsy; Intellectual disability; Microcephaly; Neurodevelopment; SynGAP; Synapse; Syngap1

PMID: 29580901 DOI: 10.1016/j.mcn.2018.03.008

Publication type, Grant support

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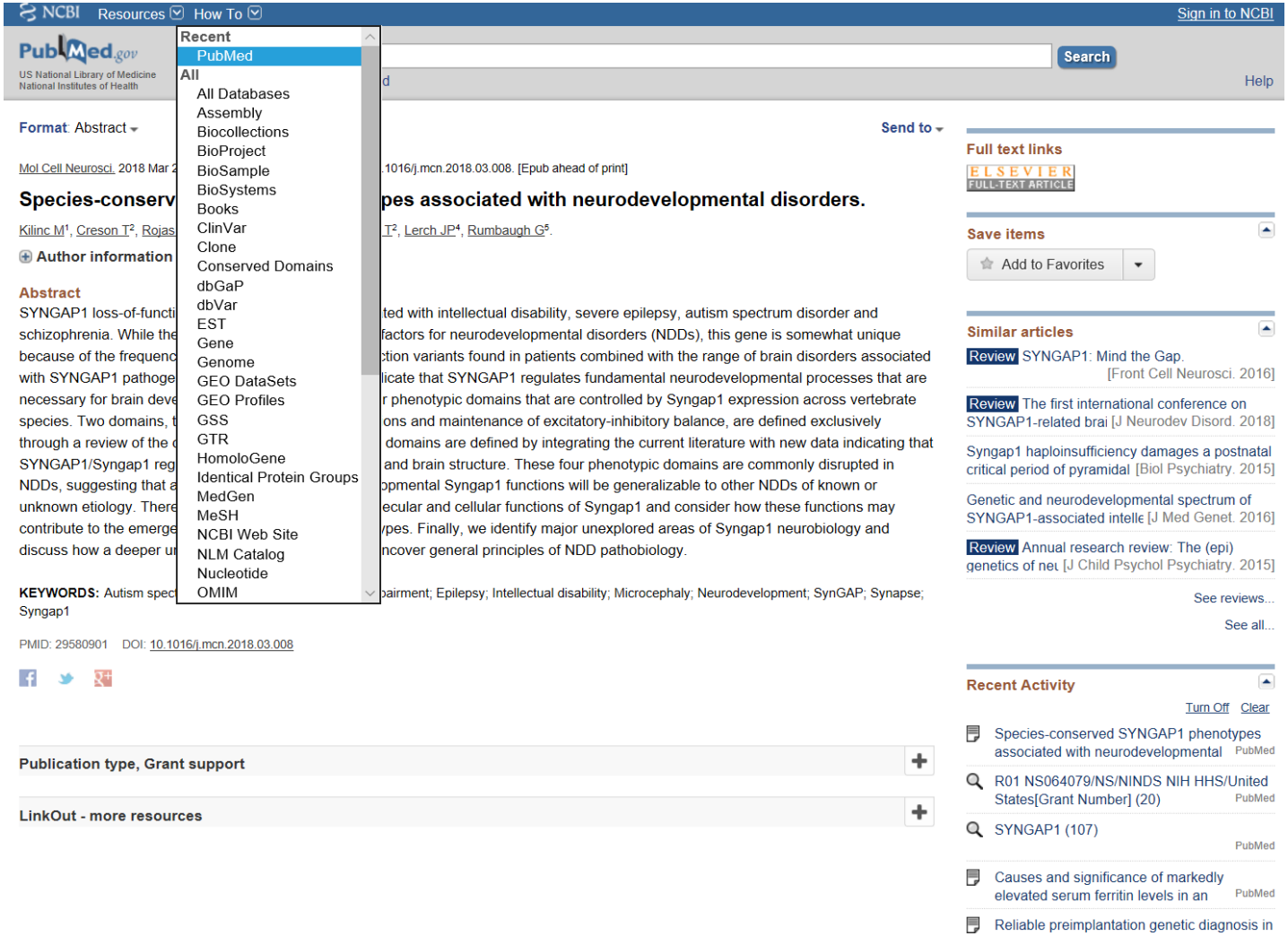

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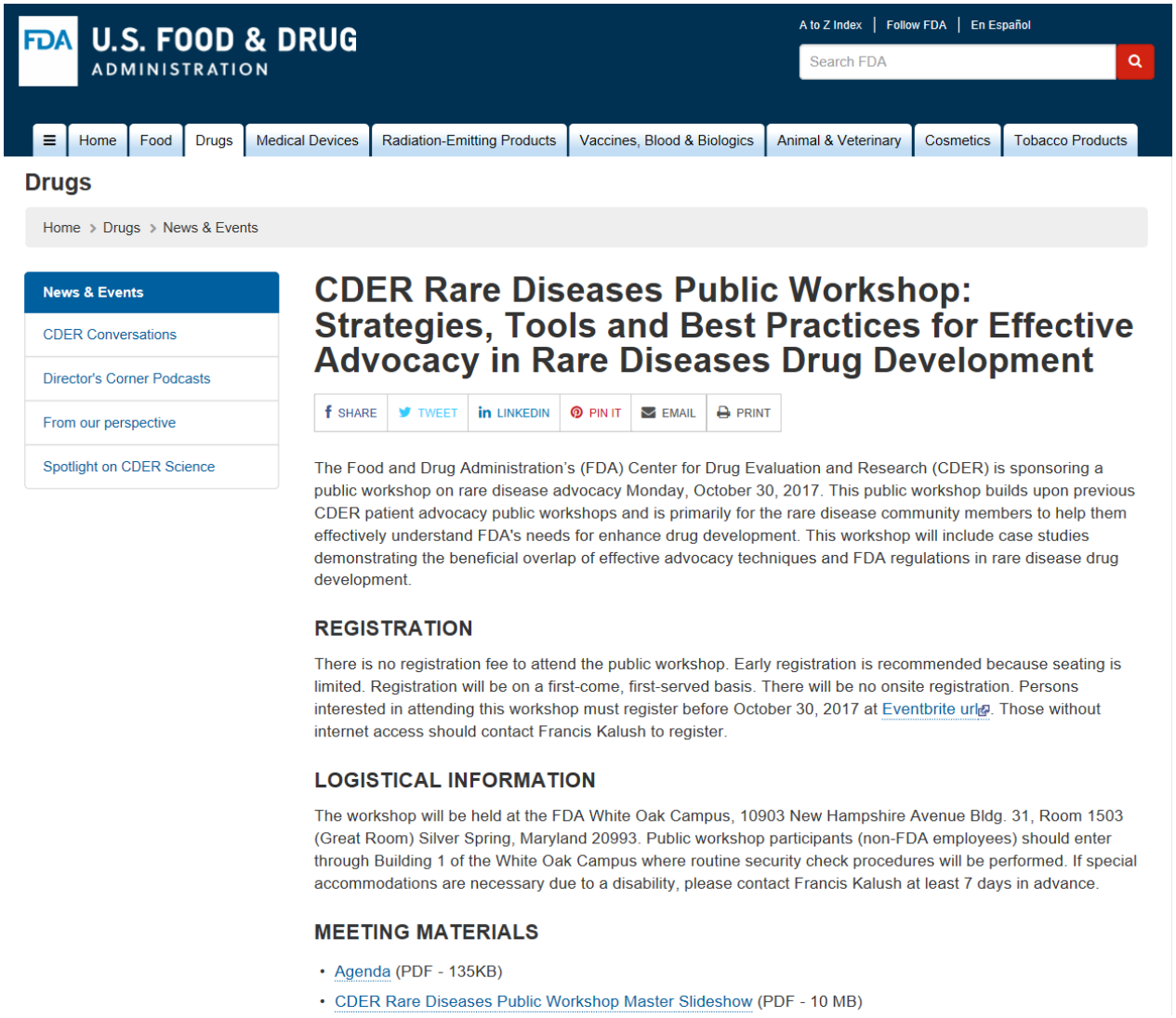
Advocate Voices Matter



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CDER Rare Diseases Public Workshop: Strategies, Tools and Best Practices for Effective Advocacy in Rare Diseases Drug Development

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The Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) is sponsoring a public workshop on rare disease advocacy Monday, October 30, 2017. This public workshop builds upon previous CDER patient advocacy public workshops and is primarily for the rare disease community members to help them effectively understand FDA's needs for enhance drug development. This workshop will include case studies demonstrating the beneficial overlap of effective advocacy techniques and FDA regulations in rare disease drug development.

REGISTRATION

There is no registration fee to attend the public workshop. Early registration is recommended because seating is limited. Registration will be on a first-come, first-served basis. There will be no onsite registration. Persons interested in attending this workshop must register before October 30, 2017 at Eventbrite url. Those without internet access should contact Francis Kalush to register.

LOGISTICAL INFORMATION

The workshop will be held at the FDA White Oak Campus, 10903 New Hampshire Avenue Bldg. 31, Room 1503 (Great Room) Silver Spring, Maryland 20993. Public workshop participants (non-FDA employees) should enter through Building 1 of the White Oak Campus where routine security check procedures will be performed. If special accommodations are necessary due to a disability, please contact Francis Kalush at least 7 days in advance.

MEETING MATERIALS

- Agenda (PDF - 135KB)
- CDER Rare Diseases Public Workshop Master Slideshow (PDF - 10 MB)

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Who is doing What?

What Research?

- Clinical trials.gov
- Epidemiology, such as a Registry
- Basic Science
- Clinical Research

Who is doing it?

- Google
- Pubmed
- NIH reporter

Look at what others have done

- Leslie Gordon, MD PhD and the Progeria Research Foundation and their approach
    - Registry
    - Cell and Tissue Bank
    - Medical and Research Database
    - Diagnostics Testing Program

Talk to the best

- Is an opinion leader near you?
- Is a specific medical researcher near you?
- BRIMR.org
- NIH reporter

3754 Brevard Road
Suite 116, Box 19
Horse Shoe, NC 28742
e-mail: rrj@brimr.org

From the Blue Ridge Institute for Medical Research (BRIMR.ORG)

Ranking Tables of NIH Funding to US Medical Schools in 2017 (1 October 2016-30 September 2017) as compiled by Robert Roskoski Jr.

The Worldwide file (Table 4) contains a large number of changes that were made in the original NIH download. These changes were made for consistency. To see the nature of these changes, click here. Table 4 is the master file from which all Tables were derived (except Table 11).

Click on School or PI to download the file in Excel Format.

Basic Science Department

Anatomy/Cell Biology School PI
Biochemistry School PI
Genetics School PI
Microbiology School PI
Neurosciences School PI
Pharmacology School PI
Physiology School PI

Clinical Science Department

Anesthesiology School PI
Dermatology School PI
Emergency Medicine School PI
Family Medicine School PI
Internal Medicine School PI
Neurology School PI
Neurosurgery School PI
Obstetrics and Gynecology School PI
Ophthalmology School PI
Orthopedics School PI

Clinical Science Department (cont.)

Otolaryngology School PI
Pathology School PI
Pediatrics School PI
Physical Medicine School PI
Psychiatry School PI
Public Health School PI
Radiology School PI
Surgery School PI
Urology School PI

Gentlemen, we've run out of money. It's time to start thinking. – Ernest Rutherford
Facts are the enemy of truth. – Donald Quixote from the musical "Man of La Mancha."
The most powerful way devised by humans for finding new facts is the experimental method. – Louis F. Leloir
Progress is made by young scientists who carry out experiments that old scientists said wouldn't work. – Frank Westheimer
Nothing in life is so exhilarating as to be shot at without result. – Sir Winston Churchill
Please do not shoot the pianist. He is doing his best. – Oscar Wilde

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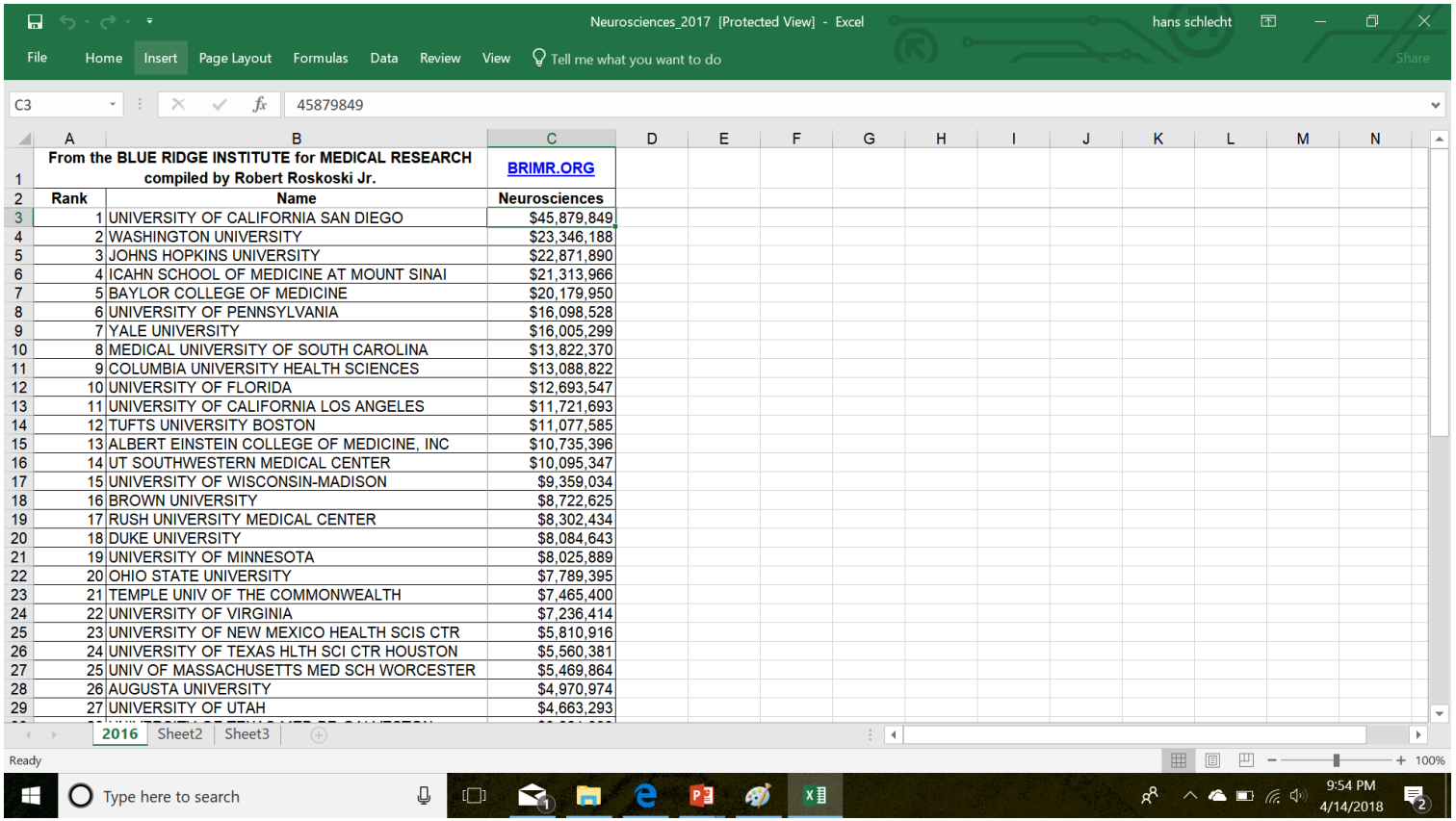

Neurosciences_2017 [Protected View] - Excel

hans schlecht

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	A	B	C
1	From the BLUE RIDGE INSTITUTE for MEDICAL RESEARCH compiled by Robert Roskoski Jr.		BRIMR.ORG
2	Rank	Name	Neurosciences
3	1	UNIVERSITY OF CALIFORNIA SAN DIEGO	$45,879,849
4	2	WASHINGTON UNIVERSITY	$23,346,188
5	3	JOHNS HOPKINS UNIVERSITY	$22,871,890
6	4	ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI	$21,313,966
7	5	BAYLOR COLLEGE OF MEDICINE	$20,179,950
8	6	UNIVERSITY OF PENNSYLVANIA	$16,098,528
9	7	YALE UNIVERSITY	$16,005,299
10	8	MEDICAL UNIVERSITY OF SOUTH CAROLINA	$13,822,370
11	9	COLUMBIA UNIVERSITY HEALTH SCIENCES	$13,088,822
12	10	UNIVERSITY OF FLORIDA	$12,693,547
13	11	UNIVERSITY OF CALIFORNIA LOS ANGELES	$11,721,693
14	12	TUFTS UNIVERSITY BOSTON	$11,077,585
15	13	ALBERT EINSTEIN COLLEGE OF MEDICINE, INC	$10,735,396
16	14	UT SOUTHWESTERN MEDICAL CENTER	$10,095,347
17	15	UNIVERSITY OF WISCONSIN-MADISON	$9,359,034
18	16	BROWN UNIVERSITY	$8,722,625
19	17	RUSH UNIVERSITY MEDICAL CENTER	$8,302,434
20	18	DUKE UNIVERSITY	$8,084,643
21	19	UNIVERSITY OF MINNESOTA	$8,025,889
22	20	OHIO STATE UNIVERSITY	$7,789,395
23	21	TEMPLE UNIV OF THE COMMONWEALTH	$7,465,400
24	22	UNIVERSITY OF VIRGINIA	$7,236,414
25	23	UNIVERSITY OF NEW MEXICO HEALTH SCIS CTR	$5,810,916
26	24	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON	$5,560,381
27	25	UNIV OF MASSACHUSETTS MED SCH WORCESTER	$5,469,864
28	26	AUGUSTA UNIVERSITY	$4,970,974
29	27	UNIVERSITY OF UTAH	$4,663,293

2016 Sheet2 Sheet3

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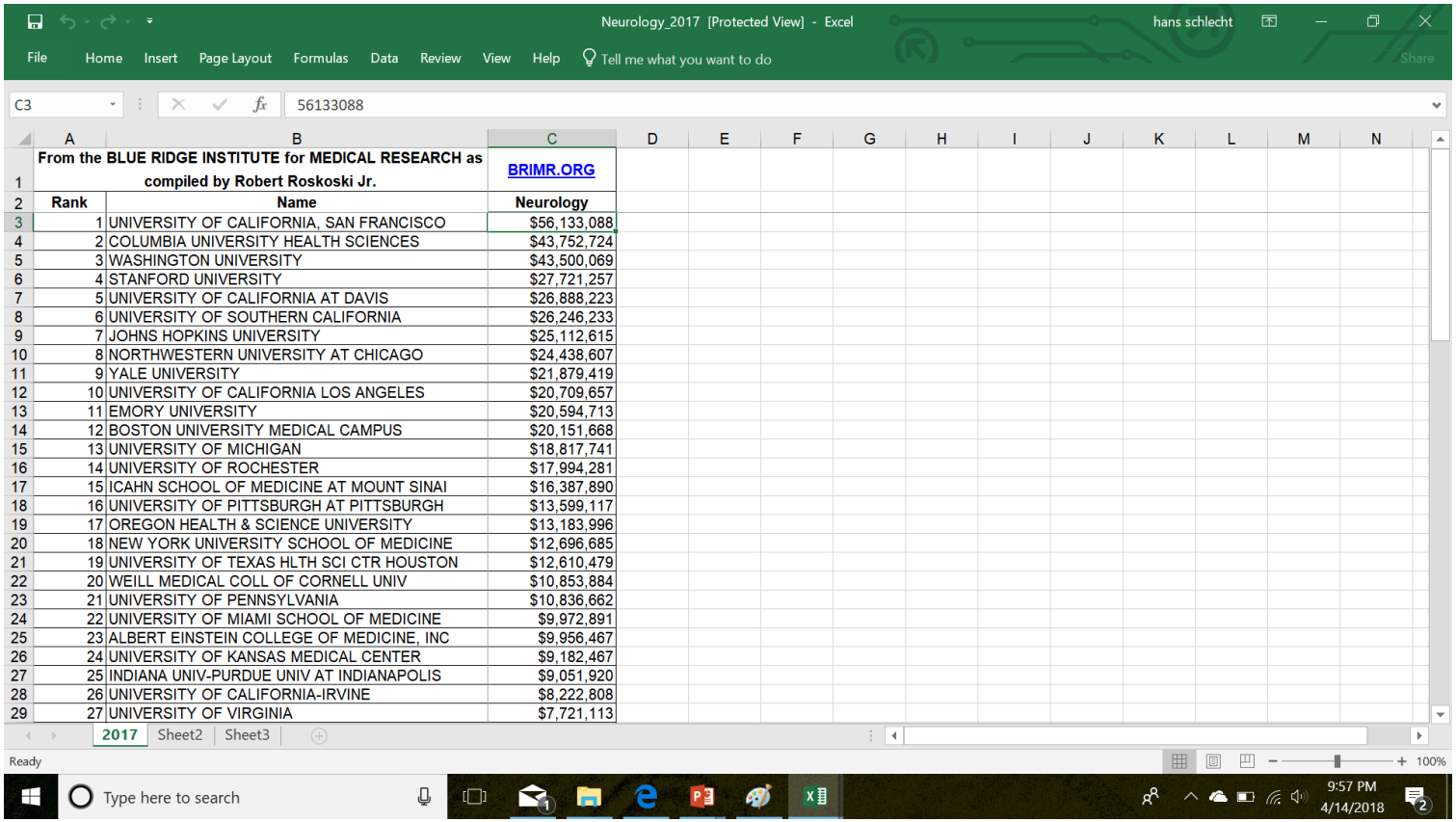

Neurology_2017 [Protected View] - Excel

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	From the BLUE RIDGE INSTITUTE for MEDICAL RESEARCH as compiled by Robert Roskoski Jr.		BRIMR.ORG
2	Rank	Name	Neurology
3	1	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	$56,133,088
4	2	COLUMBIA UNIVERSITY HEALTH SCIENCES	$43,752,724
5	3	WASHINGTON UNIVERSITY	$43,500,069
6	4	STANFORD UNIVERSITY	$27,721,257
7	5	UNIVERSITY OF CALIFORNIA AT DAVIS	$26,888,223
8	6	UNIVERSITY OF SOUTHERN CALIFORNIA	$26,246,233
9	7	JOHNS HOPKINS UNIVERSITY	$25,112,615
10	8	NORTHWESTERN UNIVERSITY AT CHICAGO	$24,438,607
11	9	YALE UNIVERSITY	$21,879,419
12	10	UNIVERSITY OF CALIFORNIA LOS ANGELES	$20,709,657
13	11	EMORY UNIVERSITY	$20,594,713
14	12	BOSTON UNIVERSITY MEDICAL CAMPUS	$20,151,668
15	13	UNIVERSITY OF MICHIGAN	$18,817,741
16	14	UNIVERSITY OF ROCHESTER	$17,994,281
17	15	ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI	$16,387,890
18	16	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	$13,599,117
19	17	OREGON HEALTH & SCIENCE UNIVERSITY	$13,183,996
20	18	NEW YORK UNIVERSITY SCHOOL OF MEDICINE	$12,696,685
21	19	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON	$12,610,479
22	20	WEILL MEDICAL COLL OF CORNELL UNIV	$10,853,884
23	21	UNIVERSITY OF PENNSYLVANIA	$10,836,662
24	22	UNIVERSITY OF MIAMI SCHOOL OF MEDICINE	$9,972,891
25	23	ALBERT EINSTEIN COLLEGE OF MEDICINE, INC	$9,956,467
26	24	UNIVERSITY OF KANSAS MEDICAL CENTER	$9,182,467
27	25	INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS	$9,051,920
28	26	UNIVERSITY OF CALIFORNIA-IRVINE	$8,222,808
29	27	UNIVERSITY OF VIRGINIA	$7,721,113

2017 Sheet2 Sheet3

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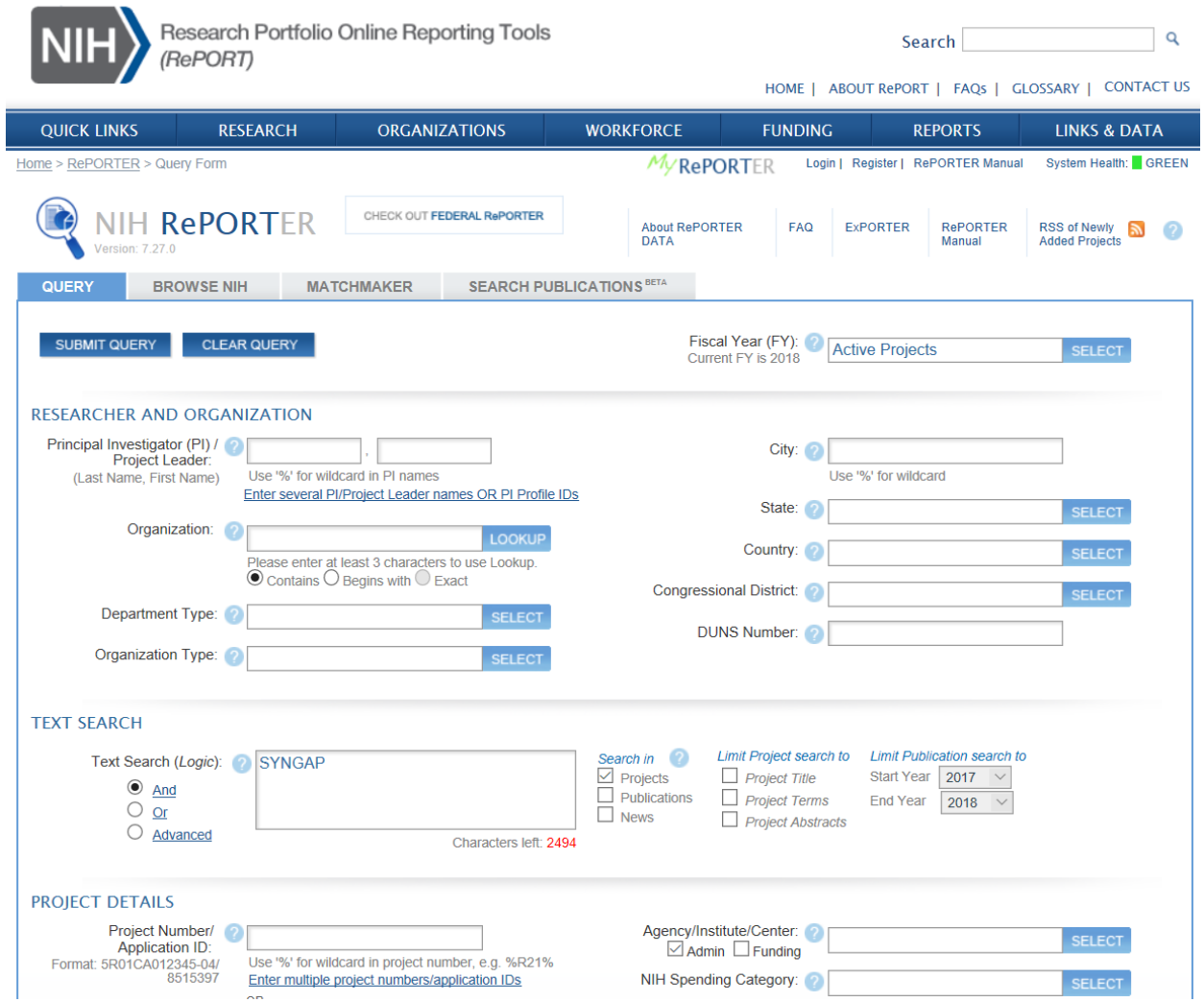

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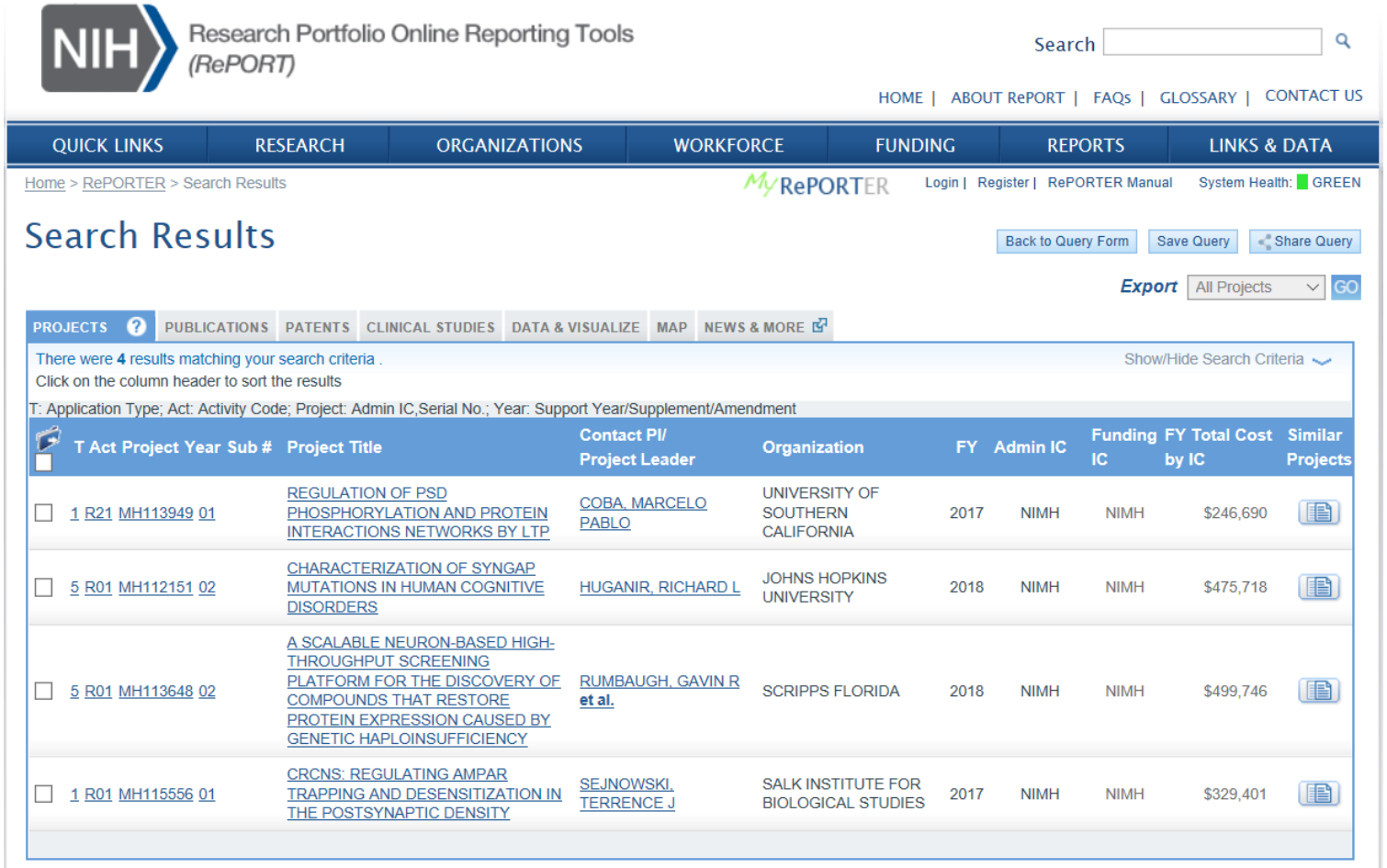

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1	R21	MH113949	01		REGULATION OF PSD PHOSPHORYLATION AND PROTEIN INTERACTIONS NETWORKS BY LTP	COBA, MARCELO PABLO	UNIVERSITY OF SOUTHERN CALIFORNIA	2017	NIMH	NIMH	$246,690	
5	R01	MH112151	02		CHARACTERIZATION OF SYNGAP MUTATIONS IN HUMAN COGNITIVE DISORDERS	HUGANIR, RICHARD L	JOHNS HOPKINS UNIVERSITY	2018	NIMH	NIMH	$475,718	
5	R01	MH113648	02		A SCALABLE NEURON-BASED HIGH-THROUGHPUT SCREENING PLATFORM FOR THE DISCOVERY OF COMPOUNDS THAT RESTORE PROTEIN EXPRESSION CAUSED BY GENETIC HAPLOINSUFFICIENCY	RUMBAUGH, GAVIN R et al.	SCRIPPS FLORIDA	2018	NIMH	NIMH	$499,746	
1	R01	MH115556	01		CRCNS: REGULATING AMPAR TRAPPING AND DESENSITIZATION IN THE POSTSYNAPTIC DENSITY	SEJNOWSKI, TERRENCE J	SALK INSTITUTE FOR BIOLOGICAL STUDIES	2017	NIMH	NIMH	$329,401	

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R21MH113949-01

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Project Number: 1R21MH113949-01
Title: REGULATION OF PSD PHOSPHORYLATION AND PROTEIN INTERACTIONS NETWORKS BY LTP

Contact PI / Project Leader: COBA, MARCELO PABLO
Awardee Organization: UNIVERSITY OF SOUTHERN CALIFORNIA

Abstract Text:

The activation of NMDAR by patterns of synaptic activity during long-term potentiation (LTP) is thought to regulate a number of protein kinases that potentiate synaptic transmission by phosphorylating proteins within the postsynaptic density (PSD). At the PSD of excitatory glutamatergic synapse, these phosphorylated proteins are thought to associate in protein interaction networks. These networks can convey important mechanism for processing, integrating and storing information at synapses in health and disease states. However, only a small number of phosphorylation sites are known. Moreover, there is no information on how NMDAR dependent high frequency stimulation-LTP modulates protein phosphorylation networks in temporal health and disease states. Our primary objectives here are to determine the temporal and NMDAR dependent phosphorylation networks triggered by the induction of LTP, and identify how synaptic stimulation in the presence of β-adrenergic receptor agonists regulates patterns of synaptic activity and protein interactions in the PSD, of both wild type and **SYNGAP** mutant mice, a mouse model of intellectual disability. For this purpose we will use a combination of mouse hippocampus CA1 mini-slices, mass spectrometry, bioinformatics and mouse genetics. This will allow a better understanding of the role of the **SYNGAP** mutation in the composition of PSD networks and the convergence of NMDAR and β-adrenergic receptors in LTP signaling networks and will inform future studies to be able to manipulate and regulate PSD signaling.

Public Health Relevance Statement:

Although a small number of proteins within the postsynaptic density (PSD) of excitatory synapses are known to be phosphorylated following LTP induction, the PSD is composed of more than 1,500 proteins that contain 100's of phosphorylation sites. The proposed research will increase our understanding of the molecular changes that are regulated by LTP, and how they are modulated by mutations associated to intellectual disability. This will allow the identification of novel proteins and signaling processes involved in synaptic plasticity, ID, and neuromodulation that will facilitate the development of future, hypothesis driven experiments.

Project Terms:

Address; Adrenergic Agents; Adrenergic beta-Agonists; Autistic Disorder; Bathing; beta-adrenergic receptor; Bioinformatics; Brain Diseases; Cell physiology; Complex; density; Development; Disease; Excitatory Synapse; experimental study; Exposure to; Frequencies; Future; Genes; Genetic; Glutamates; Health; Hippocampus (Brain); Impairment; In Vitro; Intellectual functioning disability; Link; Long-Term Potentiation; Mass Spectrum Analysis; Mediating; Modeling; Molecular; mouse model; Mus; mutant; Mutant Strains Mice; Mutation; N-Methyl-D-Aspartate Receptors; Neurons; neuroregulation; NMDA receptor antagonist; novel; Pattern; Phosphorylation; Phosphorylation Site; postsynaptic; postsynaptic density protein; Preparation; Process; protein activation; protein complex; Protein Kinase; Protein Kinase Protein Phosphorylation; Proteins; Publishing; ras GTPase-Activating Proteins; Receptor Activation; Regulation; Research; Role; Sampling; Signal Pathway; Signal Transduction; Site; Slice; Synapses; Synaptic plasticity; Synaptic Transmission; Techniques; Time

Examples of Where

- Local, Regional, National and International Conferences
- Parenting Meet-ups
- FDA Seminars
- Get out there and talk
  - Be open-minded
  - Trust but verify
  - Keep a rolodex of the earnest
  - Keep in touch with people impacting your field

Example: Clinical Research

- Ataluren for nonsense readthrough
  - Requests to PTC Therapeutics for expanded access with a back-up plan of personal use importation
  - 3rd Request approved and with the effort of Dr Poduri and her team, FDA approval and Boston Childrens IRB approval was secured and Erich began ataluren on March 25, 2018.

Example: Translational Research

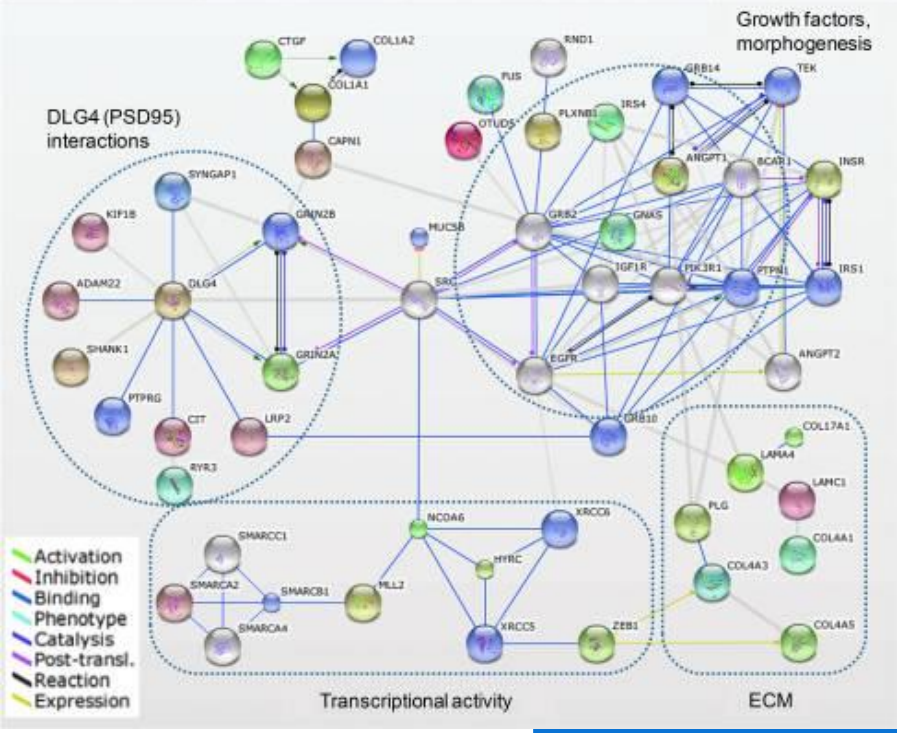
- Reached out to Dr Coba of USC
- Met and he offered to look at my son's mutation in stem cells
- Blood draw at CHB and sent to USC via IRB approved research and MTA
- Extreme Parenting Meet-up at JHU
- Learn about Payton
- Connect them to Dr Coba
- Dr Coba now is looking at her mutation and writing grants to study the differences

Biomarker

- CSF proteome
- Urine Proteome
- Plasma Proteome

Four distinct activity networks of interest were related to outgrowth, guidance and morphogenesis, the ECM, transcriptional activity, and postsynaptic density interaction. This later network included peptides from several major components of the excitatory glutamate receptor complex, including glutamate receptor 2A and B (Grin2A/B), synaptic Ras GTPase activating protein 1(Syngap1), and SH3 ankyrin repeat domain 1 (Shank1). Taken together, these results provide a mechanistic link with neuroplastic dynamics.

Name	Class	ID	Qty	P-value
DLG4 (PSD95) binding/activity partners	Interactions	Int:DLG4	8	$2.47e^{-3}$
Ncam signaling for neurite out-growth	Reactome	MSigDB:375165	7	$5.65e^{-5}$
Involved in axon guidance	Reactome	MSigDB:422475	8	$1.75e^{-3}$
Proteinaceous extracellular matrix	Cell Comp.	GO:0005578	18	$5.86e^{-9}$
Tissue development	Bio. Process	GO:0009888	24	$1.18e^{-3}$
Cell projection morphogenesis	Bio. Process	GO:0048858	15	$2.78e^{-2}$
Extracellular matrix structural constituents	Mol. Function	GO:0005201	10	$1.63e^{-8}$
Growth factor binding	Mol. Function	GO:0019838	6	$3.87e^{-2}$

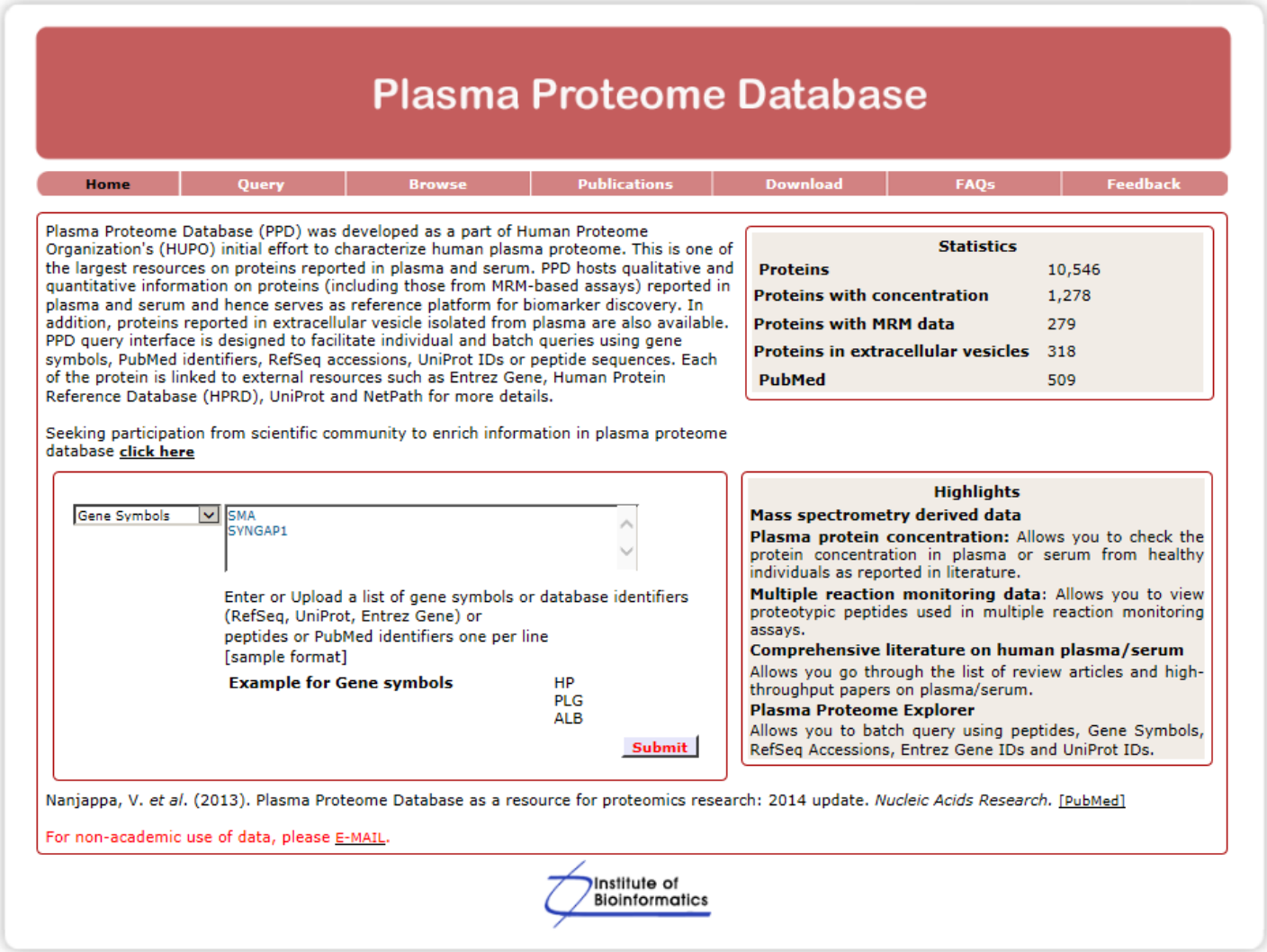


J Neurotrauma. 2014 Apr 15;31:782.

#PennMedMDBR2018 #GGPennRareSymposium

RARE PATIENT ADVOCACY SYMPOSIUM

Is SYNGAP in the blood?



Plasma Proteome Database

Home | Query | Browse | Publications | Download | FAQs | Feedback

Plasma Proteome Database (PPD) was developed as a part of Human Proteome Organization's (HUPO) initial effort to characterize human plasma proteome. This is one of the largest resources on proteins reported in plasma and serum. PPD hosts qualitative and quantitative information on proteins (including those from MRM-based assays) reported in plasma and serum and hence serves as reference platform for biomarker discovery. In addition, proteins reported in extracellular vesicle isolated from plasma are also available. PPD query interface is designed to facilitate individual and batch queries using gene symbols, PubMed identifiers, RefSeq accessions, UniProt IDs or peptide sequences. Each of the protein is linked to external resources such as Entrez Gene, Human Protein Reference Database (HPRD), UniProt and NetPath for more details.

Seeking participation from scientific community to enrich information in plasma proteome database **click here**

Statistics

Proteins	10,546
Proteins with concentration	1,278
Proteins with MRM data	279
Proteins in extracellular vesicles	318
PubMed	509

Gene Symbols

SMA
SYNGAP1

Enter or Upload a list of gene symbols or database identifiers (RefSeq, UniProt, Entrez Gene) or peptides or PubMed identifiers one per line
[sample format]

Example for Gene symbols

HP
PLG
ALB

Submit

Highlights

Mass spectrometry derived data

Plasma protein concentration: Allows you to check the protein concentration in plasma or serum from healthy individuals as reported in literature.

Multiple reaction monitoring data: Allows you to view proteotypic peptides used in multiple reaction monitoring assays.

Comprehensive literature on human plasma/serum

Allows you go through the list of review articles and high-throughput papers on plasma/serum.

Plasma Proteome Explorer

Allows you to batch query using peptides, Gene Symbols, RefSeq Accessions, Entrez Gene IDs and UniProt IDs.

Nanjappa, V. *et al.* (2013). Plasma Proteome Database as a resource for proteomics research: 2014 update. *Nucleic Acids Research.* [PubMed]

For non-academic use of data, please E-MAIL.

Institute of Bioinformatics

#PennMedMDBR2018 #GGPennRareSymposium

RARE PATIENT ADVOCACY SYMPOSIUM

Yes it is.

Plasma Proteome Database

Home | Query | Browse | Publications | Download | FAQs | Feedback

PPD ID	Gene symbol	Gene name	Entrez gene ID
HPRD_16018	SYNGAP1	synaptic Ras GTPase activating protein 1	8831

No hit in database

SMA

RARE PATIENT ADVOCACY SYMPOSIUM

Plasma Proteome Database

Home | Query | Browse | Publications | Download | FAQs | Feedback

Biological process	Cell communication ; Signal transduction
Molecular function	GTPase activator activity

Protein synaptic Ras GTPase activating protein 1 **Gene symbol** *SYNGAP1*

Cellular component

Component
Cytoplasmic vesicle GO

Experimental evidence

Total number of studies : 3

Peptide sequence	Method	Platform	Sample	Reference
	Mass spectrometry		Plasma	Liu *et al.* 2007
	Mass spectrometry	LCQ Deca XP	Serum	Barnea *et al.* 2005
	Mass spectrometry	IMS-TOF	Plasma	Valentine *et al.* 2006

RARE PATIENT ADVOCACY SYMPOSIUM

Mapping the Human Plasma Proteome by SCX-LC-IMS-MS

Xiaoyun Liu,[a] Stephen J. Valentine,[b] Manolo D. Plasencia,[a] Sarah Trimpin,[a] Stephen Naylor,[b] and David E. Clemmer[a]

[a] Department of Chemistry, Indiana University, Bloomington, Indiana, USA
[b] Predictive Physiology and Medicine Inc., Bloomington, Indiana, USA

TABLE S5. List of top 300 proteins identified in IMS-MS analysis of human plasma found in the HUPO high confidence dataset (3020 proteins)

	Acc. #[a]	Protein Name[a]	Σ Hits[b]	1[c]	2	3	4	5	Peptides$_{HUPO}$[d]
1	P02647	Apolipoprotein A-I precursor (Apo-AI) (ApoA-I)	930	218	241	212	112	147	78
2	P01024	Complement C3 precursor [Contains: C3a anaphylato:	928	342	152	209	113	112	246
3	P01023	Alpha-2-macroglobulin precursor (Alpha-2-M)	686	235	84	149	116	102	207
4	P02671	Fibrinogen alpha/alpha-E chain precursor [Contains: F	491	114	102	111	74	90	65
78	P09871	Complement C1s subcomponent precursor (EC 3.4.21	35	14	6	7	2	6	36
79	P55011	Solute carrier family 12 member 2 (Bumetanide-sensit	35	4	12	10	6	3	3
80	Q96L73	Nuclear receptor binding SET domain containing prote	35	11	6	8	3	7	3
81	Q96PV0	Ras GTPase-activating protein SynGAP (Synaptic Ras	35	8	6	4	8	9	2

J Am Soc Mass Spectrom 2007, 18, 1249–1264

Thanks

- Dr Marcelo Coba
- The Durretts
- Dr Maureen Hart
- Dr Jimmy Holder
- Dr Rick Huganir
- Dr Gavin Rumbaugh
- Birgit Hutz of PTC Therapeutics
- Dr Allan Jacobson
- Dr Georg Kluger
- Dr Eric Marsh
- Dr Anna Poduri
- Catherine Shain
- Dr Rina Rosin-Arbesfeld
- Dr Roderich Vitt
- Monica Weldon

How to Begin Research Collaborations

Mary Guilfoyle

Senior Director, Oncology Compound Team Leader

Janssen Pharmaceutical

Talking points for today

- Introduction: my role at Janssen
- The SYLVANT® (siltuximab) story: a collaborative effort
- Types of collaborations
  - Patient advocacy and clinical trials
  - Investigator initiated trials
- Key learnings on building strong collaborative relationships

SYLVANT is a prescription medication. Please consult www.SYLVANT.com for full Prescribing Information, including Warnings & Precautions

My role at Janssen

- Statistician
- Operational leadership/ Project management
- Compound Development team leader

The Janssen Commitment

We develop medicines and solutions that transform individuals' lives and solve the most important unmet medical needs of our time.

Quality and safety drive every step of product design and manufacturing, which continues even after our medicines reach patients.

RARE PATIENT ADVOCACY SYMPOSIUM

Our Credo

RARE PATIENT ADVOCACY SYMPOSIUM

SYLVANT story

- SYLVANT® is a monoclonal antibody (mAb) that binds human interleukin-6 (IL-6) and has been shown to FDA approved for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV)-negative and human herpesvirus-8 (HHV-8)-negative.
- Castleman's disease, a lymphoproliferative disorder is a rare and only partially elucidated disease characterized by growth of lymphoid tissue.

SYLVANT is a prescription medication. Please consult www.SYLVANT.com for full Prescribing Information, including Warnings & Precautions

SYLVANT story

- Clinically, patients present with lymph node growth that is confined to a single location (unicentric Castleman's disease) or occurs in multiple locations (MCD).
  - Unicentric Castleman's disease is most commonly asymptomatic
  - MCD, displays a wide variety of clinical symptoms
  - MCD can occur in association with HIV and HHV-8 infection, but in the majority of patients, MCD occurs in the absence of these viral infections.

SYLVANT is a prescription medication. Please consult www.SYLVANT.com for full Prescribing Information, including Warnings & Precautions

RARE PATIENT ADVOCACY SYMPOSIUM

Registration success

- Since its initial entry to the company nearly 25 years ago, SYLVANT, now is now registered worldwide in 49 countries and currently approved in major markets, offering MCD patients a treatment for this debilitating disease.
- In collaboration with UPENN, the Castleman Disease Collaborative Network (CDCN), a world-wide organization for those patients suffering from MCD was established.
- Janssen and the CDCN drive the ongoing registry and Janssen continues to support to MCD research and development

SYLVANT is a prescription medication. Please consult www.SYLVANT.com for full Prescribing Information, including Warnings & Precautions

What drives this collaboration

- Positive data signal triggered the submission
- Patient unmet medical need
- Company commitment to research and the patient unmet medical need
- Passion
- Patience though the long haul
- Tolerance to failure

The Patient is Center

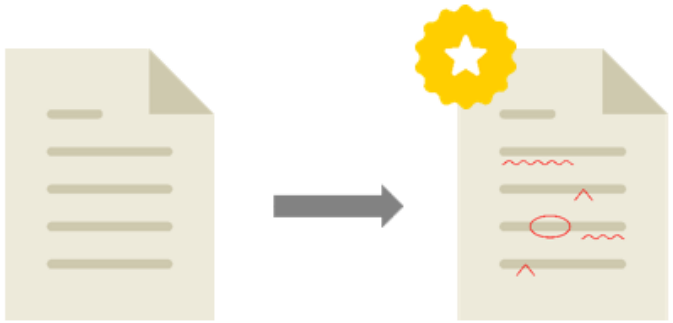
JANSSEN PATIENT ENGAGEMENT

We partner with patients and caregivers, systematically interacting directly with them. We act on patient perspectives early and maintain an ongoing dialogue to develop solutions that better meet needs.

Patient involvement

Patients are involved early and shaping solutions

Modifications to a Clinical Trial
Outcome: No dropouts



Updated Target Product Profile
Outcome: Pursuing ways to know sooner whether a treatment will work

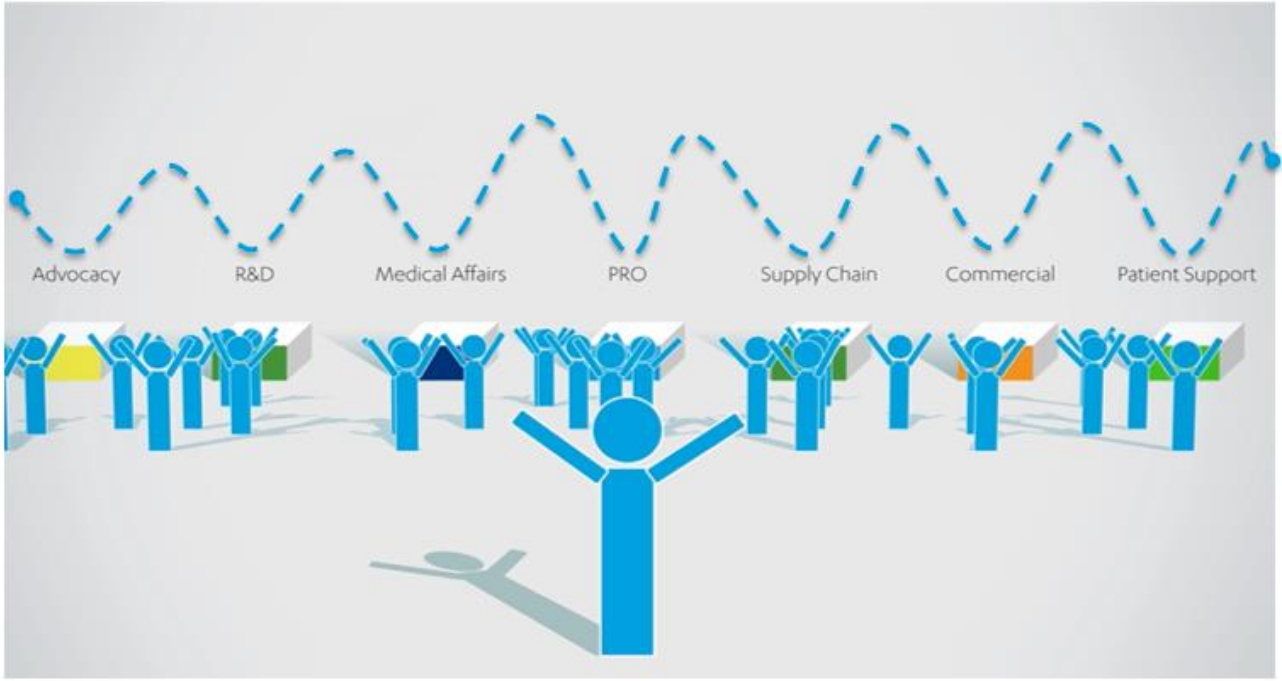
Patient Engagement : embedded

Embedded: Patient Engagement is everyone's responsibility

Global, multidisciplinary Leadership Team in place to lead change and coordinate efforts

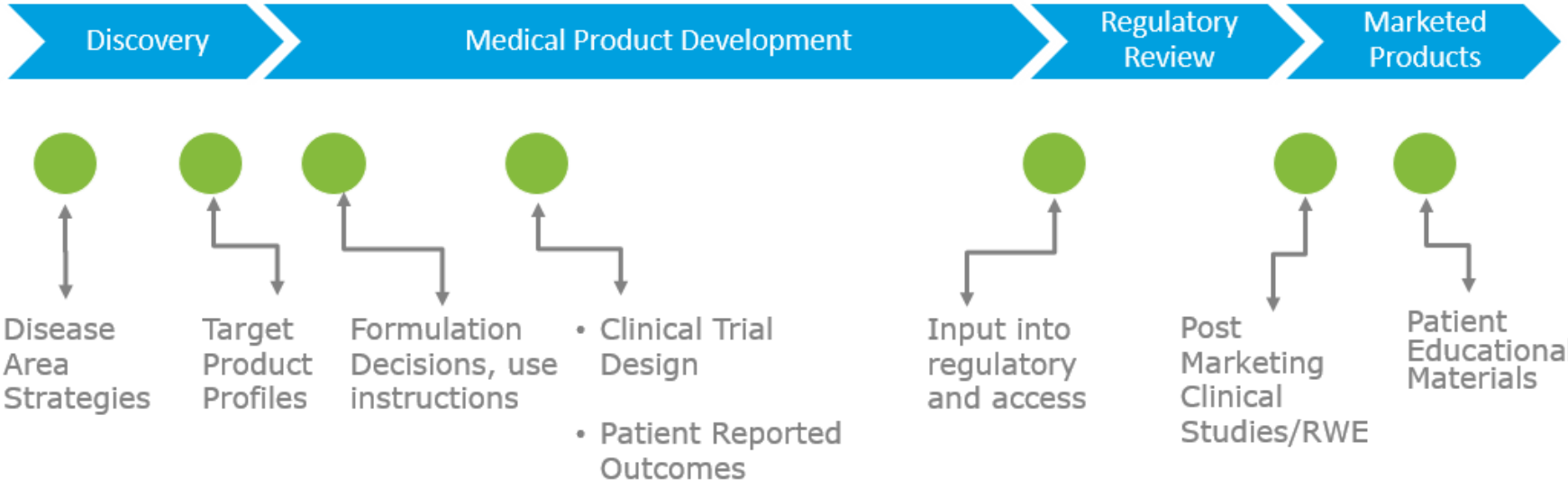
Shared commitment, new tools

Supported at the highest levels



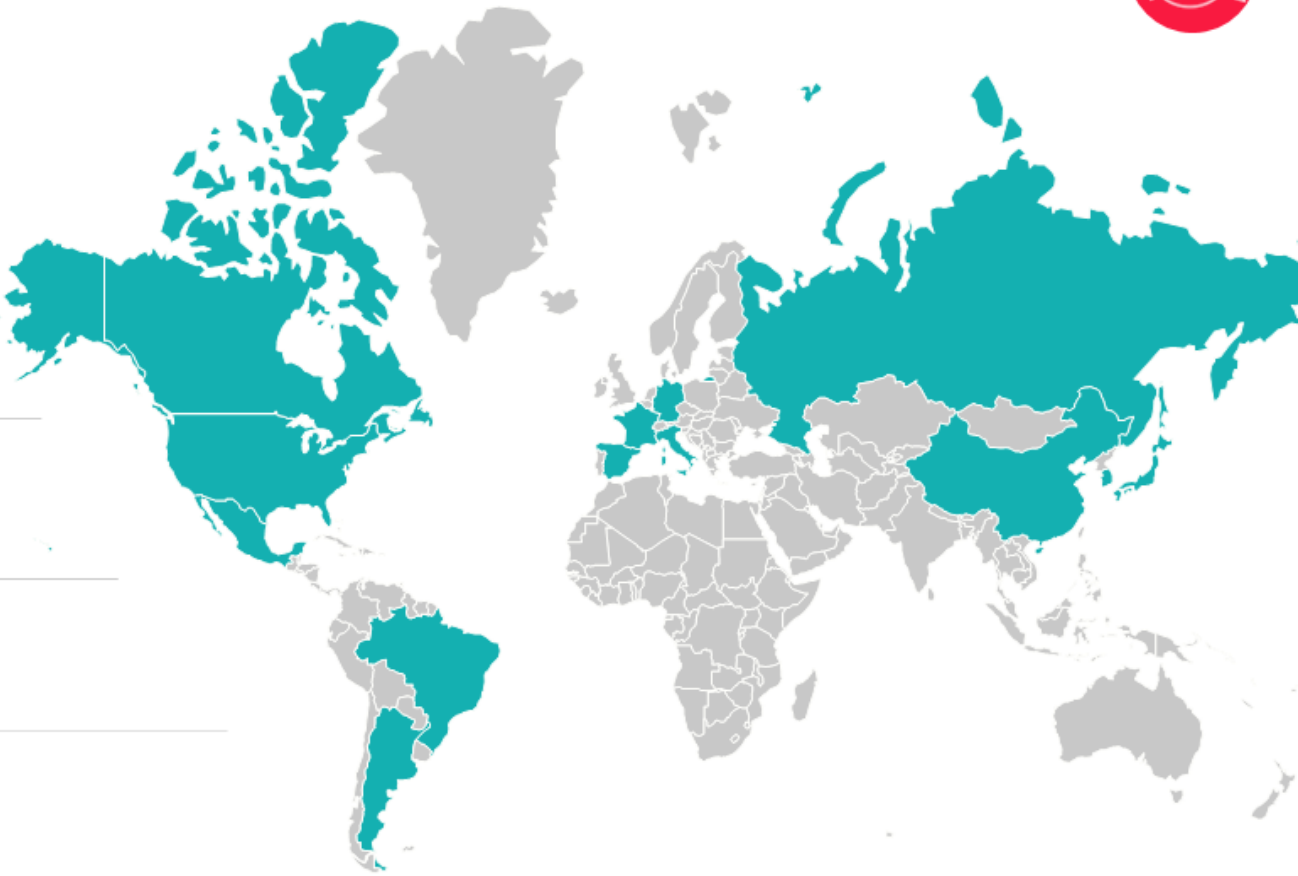
Patient Engagement: Systematic

Systematic: Patient insights are proactively incorporated early and throughout product lifecycle



Patient engagement: global

Systematic: Janssen Commitment to Patient Voice in Clinical Trials



1,300 patients

13 countries

11 Disease Area Strongholds

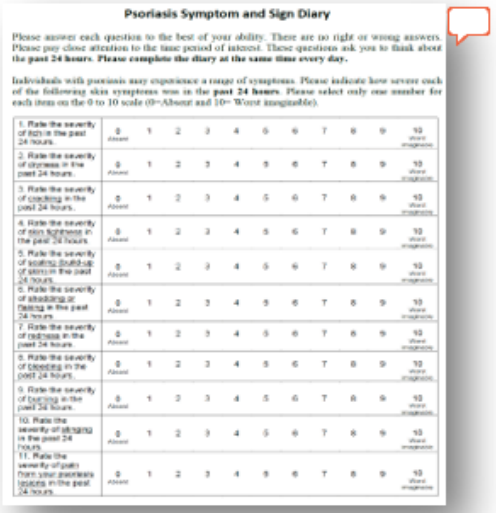
Patient Reported outcomes

Systematic: Patient Reported Outcomes (PROs) are systematically incorporated into the development process

- PROs measure how patients feel and function, reported directly by patients without interpretation by anyone else
- PRO measurement tools must be scientifically rigorous and valid

Psoriasis Symptoms & Signs Diary (PSSD)

- New PRO measurement tool developed in collaboration with patients, clinicians and Janssen with input from regulators
- Measures symptoms that matter to patients, reported by patients
- Available in 13 languages for anyone to use


Psoriasis Symptom and Sign Diary

Please answer each question to the best of your ability. There are no right or wrong answers. Please pay close attention to the time period of interest. These questions ask you to think about **the past 24 hours. Please complete the diary at the same time every day.**

Individuals with psoriasis may experience a range of symptoms. Please indicate how severe each of the following skin symptoms was in the **past 24 hours**. Please select only one number for each item on the 0 to 10 scale (0=Absent and 10= Worst imaginable).

1. Rate the severity of itch in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
2. Rate the severity of dryness in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
3. Rate the severity of cracking in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
4. Rate the severity of skin tightness in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
5. Rate the severity of scaling (build-up of skin) in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
6. Rate the severity of shedding or flaking in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
7. Rate the severity of redness in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
8. Rate the severity of bleeding in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
9. Rate the severity of burning in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
10. Rate the severity of stinging in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
11. Rate the severity of pain from your psoriasis lesions in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable

Accountability tools

Accountable: Measuring progress drives change

OBJECTIVES:

- Drive behavior to incorporate direct patient voice early
- Understand barriers

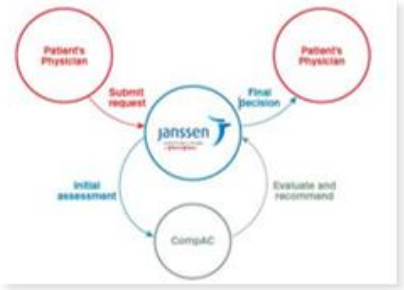
MEASUREMENT:

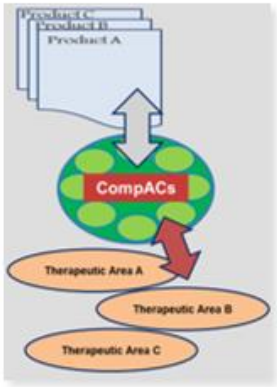
- A targeted list of high priority medicines is being measured
- Progress is reported every 6 months

JANSSEN PATIENT ENGAGEMENT DASHBOARD	
Disease Area Strategy	Integrated patient journey
	Disease area strategy
Medicine Development	Target Product Profile (TPP)
	Indication(s) and end points
	Product formulation and delivery
	Need for pre-approval access
Clinical Trial Plan	Patient insight prior to pivotal
	Protocol designs and operational strategies
	Patient Reported Outcomes

Dynamic and responsive

Dynamic: A fair, ethical approach to pre-approval access via Compassionate Use Advisory Committee (CompAC)



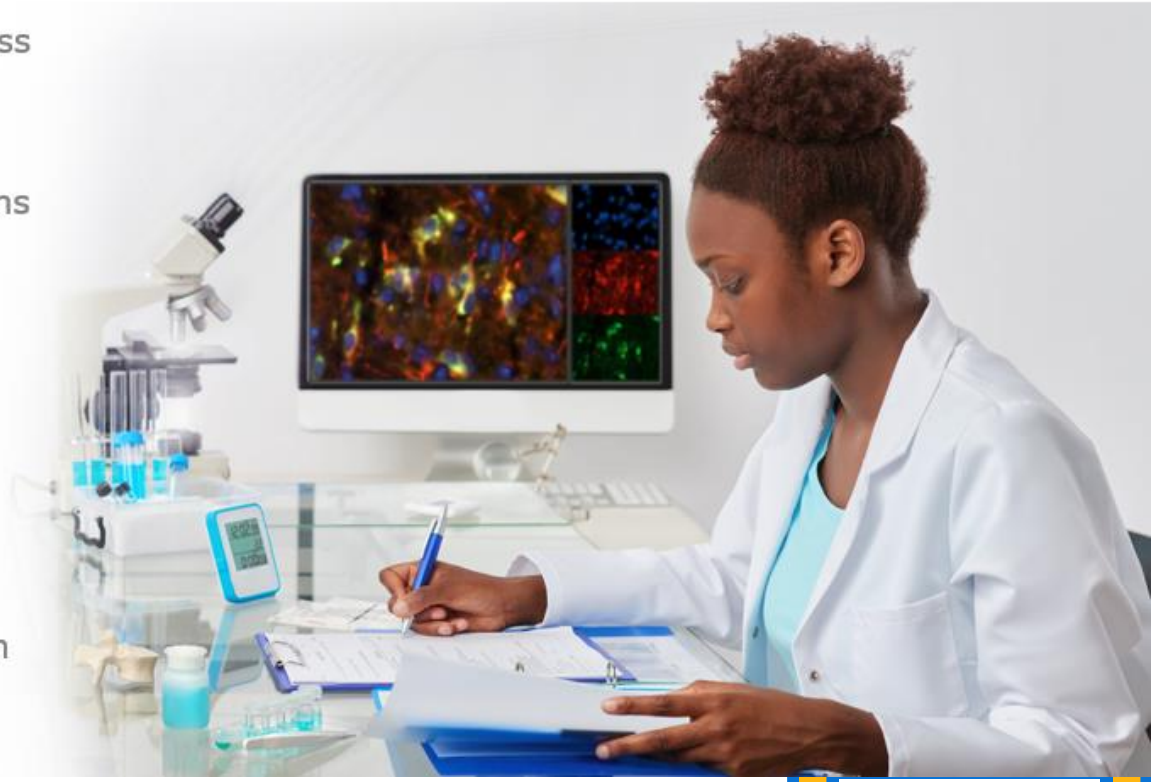


RARE PATIENT ADVOCACY SYMPOSIUM

Clinical trials

Dynamic: Clinical trials need to be accessible with a positive patient experience

- Improving trial awareness and access via Janssen Global Trial Finder
- Pursuing greater inclusion of underrepresented patient populations in trials
- Innovating clinical trials to improve patient experience
- Evaluating ways to make trial information more accessible to patients when data are available
- Publishing clinical trial results regardless of outcomes or change in status



Janssen Patient Engagement:
Working together toward patient inspired innovation

Partnering directly with patients and embedding your voice into everything we do

Delivering therapies that better meet needs to patients faster

Empowering patients to make better usage of tailored solutions

Improving Health Outcomes

More sustainable Health Care

RARE PATIENT ADVOCACY SYMPOSIUM

Isn't Clinical Research All Alike?

- **Basic science** – NIH, bench-top and other. Grant from department or government.
- **Industry (sponsored)** - initiated clinical research. FDA regulated.
  - Usually leads to marketing registration
- **Investigator-initiated research**

Who is an Investigator? (Sponsor-Investigator)

- An individual (not a corporation) who both initiates (plans and designs) and conducts an investigation, and under whose immediate direction the study drug is administered or dispensed. ***Investigator IND***.

  21 CFR 312.3 and ICH E-6 (GCPs) 1.54

  - Plans, designs, conducts, monitors, manages the data, prepares reports, and oversees all regulatory and ethical matters
  - 21 CFR §312 Subpart D

Key learnings on building collaborations

- The patient advocacy process and the IIS process are two examples of Janssen's external collaboration capabilities

Key learnings:

- There is no wrong question or answer
- Identify who you need to speak
- Be persistent
- Be more persistent, answers sometime take time to circulate to the correct person
- Decisions take time

THANK YOU !!