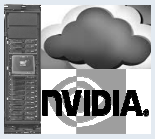
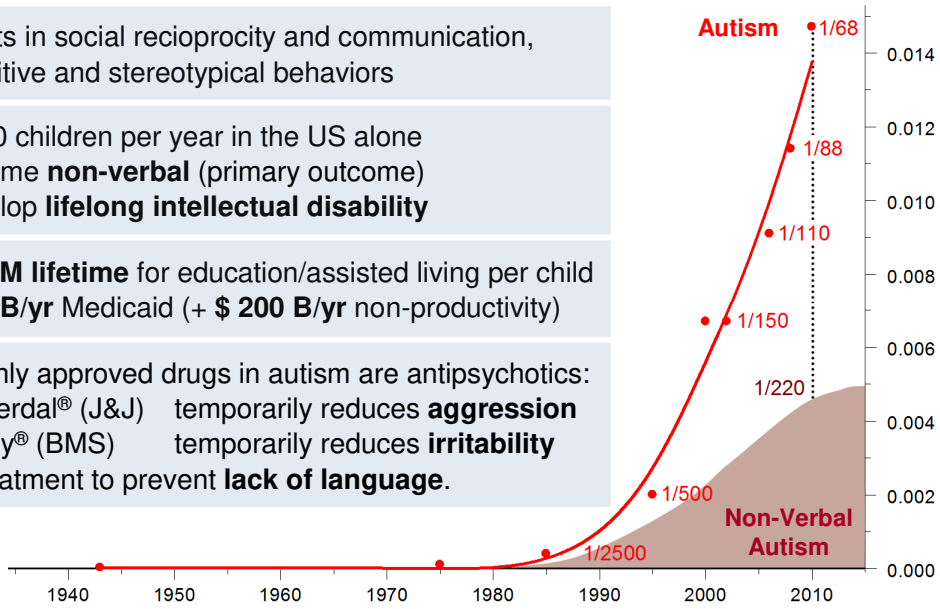
ASDERA – Overview

Mission	To bring novel drugs to market for **high unmet needs** by utilizing a computational biostatistics platform (US 7,664,616), the first to identify genetic risk factors for **complex diseases**
Drug Discovery Platform	**1800** Gauss-Legendre → **1900** Ohdner **9 Byte** **ANOVA**  **1965** IBM **256 kB** **PCA**  **1985** PC **16 MB** **Bayes**  **1948** Hoeffding → **2001** GPU **4 GB** **u-Stat** 
Time-Pipeline	Validation: Confirmation of known drug targets in **epilepsy** Proof-of-Concept: L-fucose in **Crohn's disease** (in phase 3) **Current lead:** ASD-002 against **mutism in autism** (phase 3 ready) Next drug: Preventing metastases in **breast cancer** (pat. pending) Outlook: Delaying **Alzheimer's** and **Parkinson's** (pat. pending)

ASDERA – Market Need / Opportunity

Autism	Defects in social recioprocity and communication, Repetitive and stereotypical behaviors
Incidence of DALD in autism	20,000 children per year in the US alone • become **non-verbal** (primary outcome) • develop **lifelong intellectual disability**
Economic Impact of DALD	**$ 10 M lifetime** for education/assisted living per child **$ 200 B/yr** Medicaid (+ **$ 200 B/yr** non-productivity)
Unmet need	The only approved drugs in autism are antipsychotics: • Risperdal® (J&J) temporarily reduces **aggression** • Abilify® (BMS) temporarily reduces **irritability** No treatment to prevent **lack of language**.

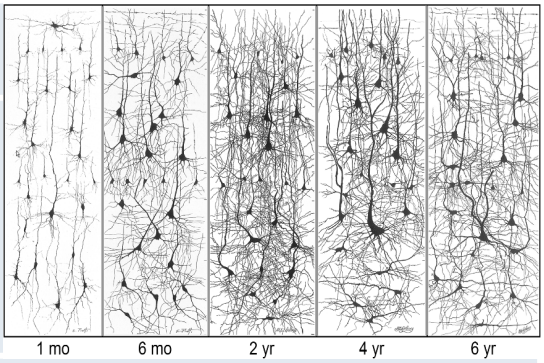


ASDERA – Overview

Focus (unmet need)	To bring the first drug to market to prevent lack-of-language in autism.
Lead Indication: Mutism [ICD F94.0] in Autism [ICD F84.0]	Disruption of Active Language Development (DALD) in toddlers developing Autism Spectrum Disorders (ASD), who • become **non-verbal** (primary outcome) (50% after speaking some words) and, thus, • develop **life-long intellectual disability** (ID) Children may still develop autism, but will be verbal ("Asperger's").
Product	ASD-002: Market-exclusive ester-prodrug of mefenamic acid (MFA)
Status	**Patent** filed in US and EU. **Orphan** Drug Designation for MFA pending Preparing CMC / manufacturing for a short **505(b)(2)** regulatory pathway for the **single phase 2b/3 trial** needed for a breakthrough drug.

ASDERA – 2nd Year of Life as the Window of Treatment Opportunity

Pathology	Cortical density declines after 24 months (of age). ⇨
Epidemiology	Cochlear implants before 24 months preserve language. Romanian orphans older then 24 months in 1990 developed "quasi-autism".
Imaging (fMRI)	"Patches of disorganization" are seen in the language cortex of non-verbal children after 24 months.
Physiology	Language regression is typically seen at 12–15 months. Early symptoms justifying a pharmaceutical intervention can only be detected from 9 months (by pediatrician at the routine "well-child visit").



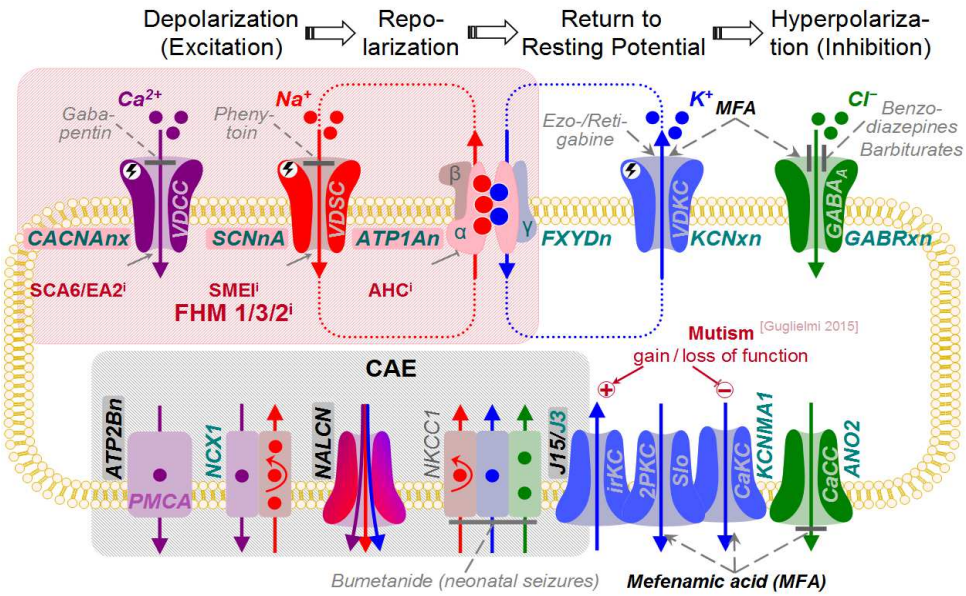
ASDERA's Novel Discovery Technology and Mefenamic Acid Hit

Discovery Platform (US 7,664,616)	The platform screens not only for individual genetic 'letter' positions (SNPs) but **genetic 'words'** (several neighboring SNPs). It also accounts for **genetic 'grammar'** (neighborhood, compound heterozygosity, recombination hotspots, ...) **within the statistical method**. Feasible only since 2001 (32-bit OS), it already yielded several hits.
Genetic results	Results from two independent ASD populations http://www.nature.com/articles/tp2013124 showed lack-of-language associated with • **Ion channels** (excitation/inhibition imbalance), including • Known **migraine** genes (FHM) and potassium (K+) channels.
Independent Confirmation	Guglielmi (2015) identified the same K^+ channels and showed • **gain**-of-function in **inward** and • **loss**-of-function in **outward** K^+ channels impairing ability of neurons to adjust to stress (hyperpolarization).
Mode of Action	Mefenamic acid prevents migraines by **activating outward** K^+ channels.

ASDERA – Ion Channel Dysfunction in Migraines / CAE / DALD

FHM 1/2/3^i: familial hemiplegic migraine
SCA6/EA2^i: ataxias
SMEI^i: severe myoclonic epilepsy
AHC^i: alternating hemiplegia of childhood
^{i}: disease of infancy

CAE: childhood absence epilepsy



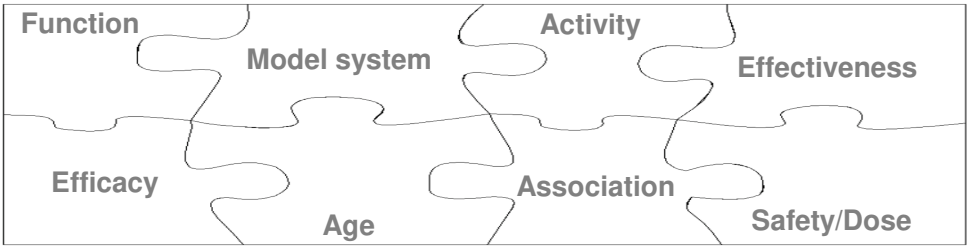
ASDERA – *in vitro* / Animal / Clinical Evidence for Efficacy of MFA

Pre-Clinical (MoA)	*in vitro*, MFA activates outward K^+ channels. (>10 studies) In mice, this reduction of hyperexcitability prevents seizures. (>7 studies)
ASD children have migraines **Migraineurs as a 'model'**	Abdominal **migraines** in ASD children turn headache **migraines** in adults. **Migraines** and DALD share • Individual and familial co-occurence • Genes (familial hemiplegic migraine, K^+ channels) • Epileptiform EEGs • Avoidance of social contacts (in autism: "regression")
Clinical Trials of MFA (PoC)	Four clinical trials have shown that MFA is effective in **migraine** • treatment and • prevention.
US approval	MFA is approved for the treatment of dysmenorrhea, including prevention of menstrual **migraines** with poor response to COX-NSAIDs.

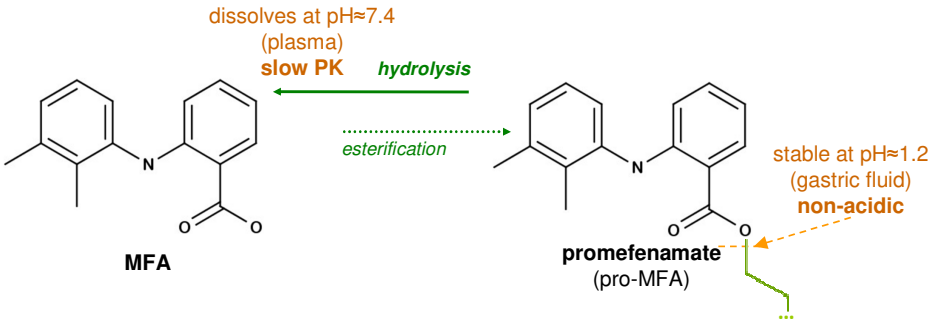
ASDERA – Safety of MFA and pro-MFA in Pediatric Use

UK Approval Pediatric Use	MFA is approved in juvenile arthritis • for chronic use • from 6 months of age.
UK Safety Data for MFA	MFA is an NSAID (like Infant Motrin®), not a 'psycho-active drug'. In 3 – 36 month old children • only 6 AEs were reported • over 50+ years of use. "no specific signal has been identified." [EMA 2012]
Improved Safety for pro-MFA	MFA, however, is known to have more side effects than other NSAIDs: • Convulsions (from accidental overdose) • Diarrhea (intestinal complications are already common in kids with ASD) • Kidney problems (from diarrhea) of Pro-MFA avoids convulsions (slow PK) and reduces diarrhea (non-acidic).

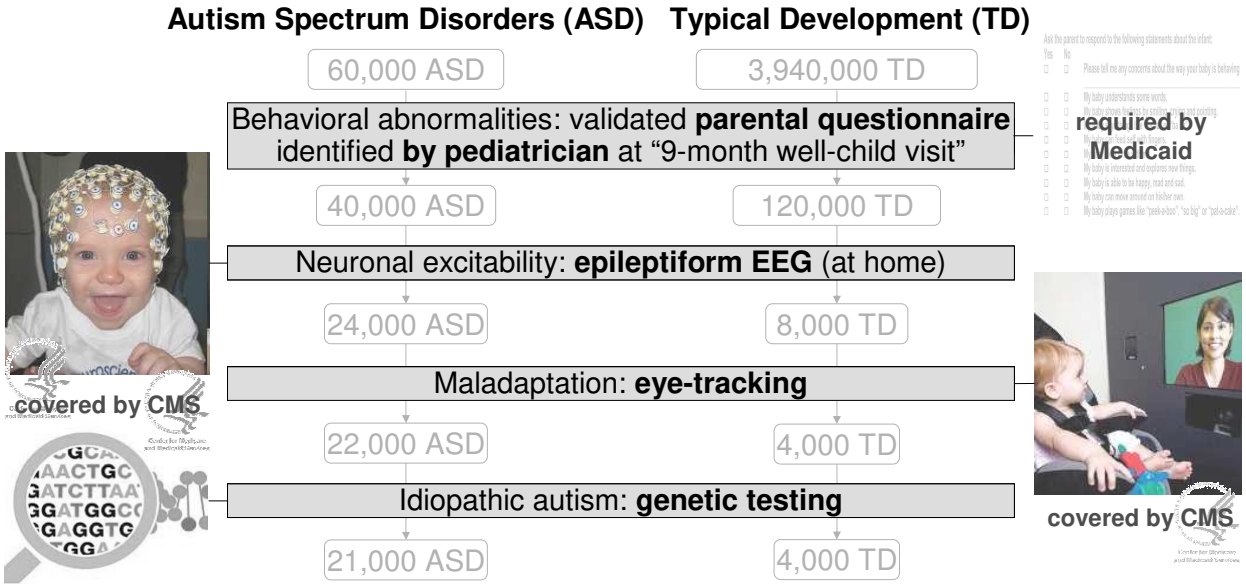
ASDERA – Scientific, Pre-clinical and Clinical Support

Human Genetics	Association:	K^+ ion channels associated with lack of language.
Published *in vitro,* animal, human **Results** **Agency findings**	Cellular defect:	K^+ outward loss-of-function causes lack-of-language.
	Activity:	MFA activates outward K^+ channels. (>10 MoA studies)
	Efficacy:	MFA prevents induced seizures. (>7 animal studies)
	Model system:	Migraineurs (co-occurance, genes, EEG, behavior).
	Effectiveness:	MFA is effective against migraines, (4 PoC studies)
	Age:	12 – 24 mo is the window of opportunity.
	Safety/dose:	50+ years of chronic use from 6 months of age.
A complete puzzle		

ASDERA – Pro-MFA Formulation / Next Stage: Single Phase 2b/3 trial

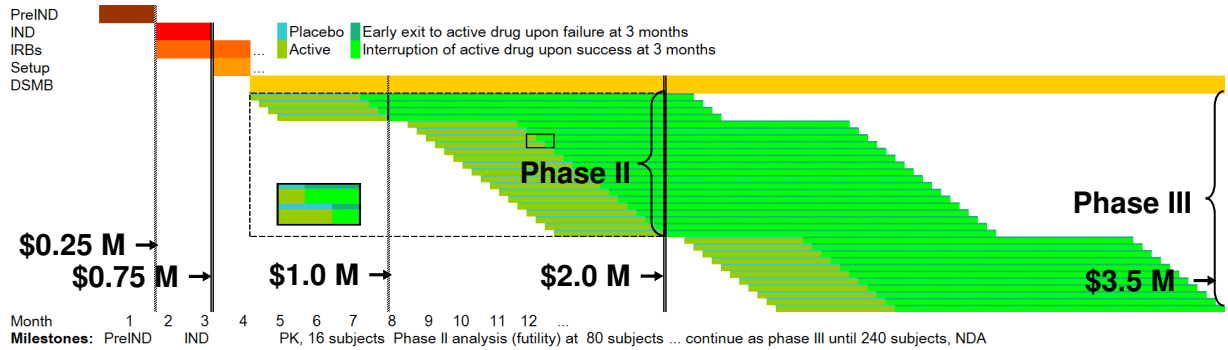
Pro-MFA **an ester of MFA**	
New Clinical Indication	FDA: "Esterification does not create a 'New Chemical Entity' " (precedent: propacetamol/Ofirmev®)
505(b)(2)	FDA: "Published results and Agency findings can be used for phase 1/2 (precedent: Abilify® in Tourette)
1st in Mutism [F94.0]	A breakthrough drug can be approved after a single phase 2b/3 trial only.

ASDERA – Market size: 25,000 US Children/yr (Orphan Indication)



ASDERA – Clinical Phase 2b/3 Trial Design / Funding Milestones

Size / Duration Primary Endpoint	240 outpatient study (conducted by a contract research organization, CRO) 12 months to primary outcome (#words spoken NCT01013545, see Ampyra®)
At 3 months	No words: Early exit to active drug (avoids child-specific IRB hurdles) Typical development: Treatment interruption (restart in case of regression).
At 80 subjects	Interim futility analysis (end of phase 2b)



ASDERA – IP Protection and Market Exclusivity

IP Protection **Market Exclusivity**	US/EU patent for fenamate derivatives$_{(IDS\ Feb\ 2017)}$, expiration 2034 Orphan drug designation$_{(amended\ Mar\ 2016)}$ pending US: 7.5 years from NDA (7 years + 0.5 years pediatric) EU: 12.0 years from NDA (10 years + 2.0 years pediatric)
No off-label use of MFA	High litigation risk for **physicians** prescribing less-safe drug to infants. No incentive for **parents** because of • health insurance for approved drugs (precedent: Avastin®) • patient assistance
No off-label use of pro-MFA	Since July 2016, FDA enforces **compounding law** (no Macena risk) Pro-MFA not approved for other indications: **no ANDA option** **Few new indications** for controlled-release NSAID (fever, pain) **Low price elasticity**: 2.5% price = 50% market (Avastin®: 50 vs 2000 USD)

ASDERA – Market Projection (Contact ASDERA for Details)

Market Size	Target Population: 50,000 children / yr (US+EU), identified at routine visit Ponstel®$_{(1965)}$: USD 36,000 / yr (q.i.d., USD 25 / pill$_{w/coupon}$)
505(b)(2) Precedents	Vyvanse$_{(2008)}$®, pro-D-amphetamine$_{(1937)}$ USD 2B$_{(2016,\ US)}$ Soolantra$_{(2015)}$®, Ivermectin$_{(1981)}$ USD 3B$_{(2016)}$
Forecasting	
Partnering Options	• Licensing • Joint Development Partnership with options for consideration: ◦ Milestones ◦ Right-to-acquire option ◦ Royalty

ASDERA – Virtual Company Team / Partners*

Management: inVentiv Health Clinical will lead FDA interactions from pre-IND to NDA and assume all management responsibilities during the trial.

Therapeutic areas: generics / pediatrics
Phase III: full range of **clinical trial services**
Consulting: small molecules / 505(b)(2)
http://www.inventivhealthclinical.com/

Knut M. Wittkowski, PhD ScD
Senior Research Associate, The Rockefeller Univ.
Director, Biostatistics, Epidemiology & **Research Design**
Center for Clinical and Translational Science
apl. Professor, Eberhard-Karls-University, Tübingen

Drug Development: Regis Technologies
Partners with pharmaceutical/biotech companies to help expedite drugs to market
cGMP Custom Services http://www.registech.com/

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Assistant Professor of **Pediatrics**
Medical Director, Inpatient Pediatrics
Director Clinical Research Center, NYU School of Medicine
PI, **Drug Development** Educational Programm (NIDDK)
New York Univ. Langone Medical Center

Orphan Drug Regulation: Bert Spilker, PhD MD
Independent Consultant on Regulatory Affairs
Clin. Professor of Pharmacy Practice, U of Minnesota
Sr. VP Scientific/Regulatory Affairs, PhRMA (1998–2001)
President/Co-founder, **sold Orphan Medical, Inc in 2005**
http://www.bertspilker.com/

John Jay Gargus, MD PhD
Professor of Pediatrics, Physiology & Biophysics
Director, Center for Autism Research and Translation
PI, **Drug Discovery** Platform for **Autism**
Univ. California Irvine

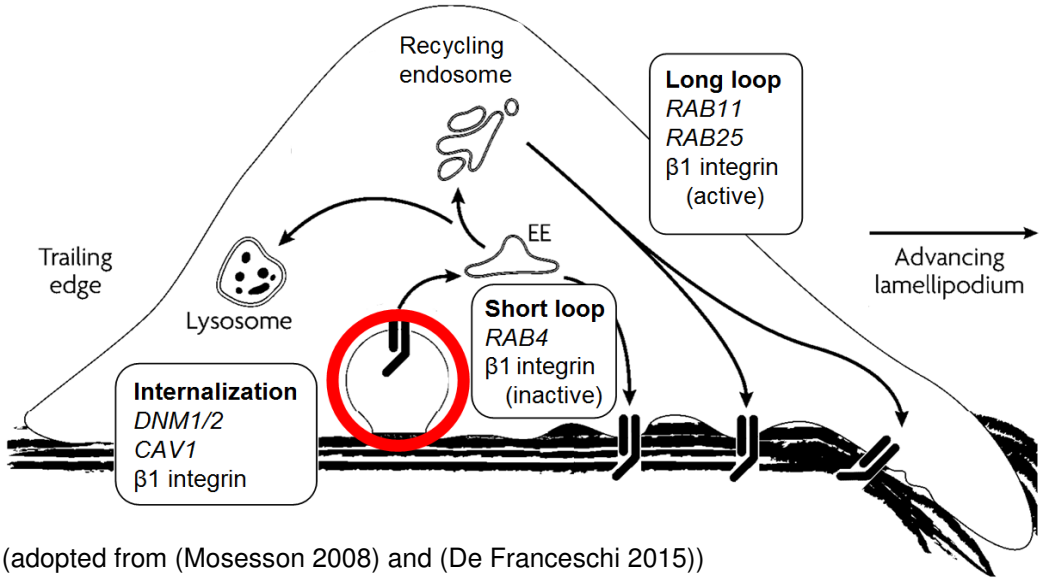
505(b)(2) Regulation: Camargo
Comprehensive drug development services specialized for the 505(b)(2) approval pathway
http://www.camargo.com/

* Terms being finalized

ASDERA – Summary

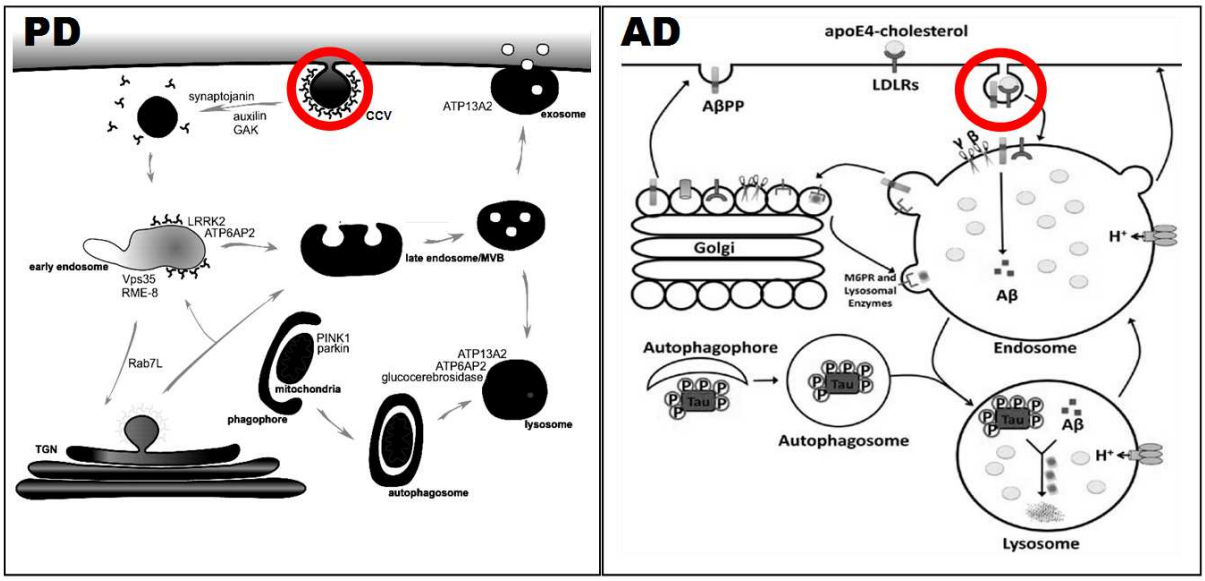
Human Genetics	Association:	K^+ ion channels associated with lack-of-language.
Published *in vitro*, animal, human **Results** **Agency findings**	Cellular defect:	K^+ outward loss-of-function causes lack-of-language.
	Activity:	MFA activates outward K^+ channels. (>10 MoA studies)
	Efficacy:	MFA prevents induced seizures. (>7 animal studies)
	Model system:	Migraineurs (co-occurance, genes, EEG, regression).
	Effectiveness:	MFA is effective against migraines, (4 PoC studies)
	Age:	12 – 24 mo is the window of opportunity.
	Safety/dose:	50+ years of chronic use from 6 months of age (UK).
Plan forward (Precedents)	FDA	505(b)(2) path for an NSAID ester prodrug (Ofirmev®, propacetamol)
	PTO	Strong IP protection (patent / orphan drug pending, see Avastin®)
		single Phase 2b/3 outpatient trial (breakthrough drug)
	$$$	2–3 years from a lucrative market (Vyvanse®, pro-amphetamine$_{(1937)}$)
Outlook		The same platform identified novel drugs in breast cancer, PD, and AD
		and identifies genetic risk factors for non-response in phase 2/3 trials.

"Derailed Endocytosis" (Mosesson 2008) in Breast Cancer (β1 Integrin)



(adopted from (Mosesson 2008) and (De Franceschi 2015))

"Derailed Endocytosis" (Van Dooren 2014) in PD (aSyn) and AD (APP)



(adapted from Schreij 2015) (adapted from Chen 2014)

BC Genes by Study/Pathway

s-values in muGWAS/ssGWAS;
top block: genes above aGWS in muGWAS (CGEM: 5.29, EPIC: 5.71, PBCS: 5.13);
bottom: genes with SNPs above aGWS in ssGWAS only (CGEM: 4.03, EPIC: 4.00, PBCS: 3.84, ssGWAS results for genes also implicated in muGWAS are shown next to the muGWAS results);
center: other genes shown in Fig 1;
Mbrn (green): membrane-associated (GPCR, FcR, HA, RTK, Ion channels),
PI/EC (pink): PIP cycle/EEC,
MPK (violet): MAP kinases,
Ncls (blue): nucleus (cell cycle control, transcription, splicing).

Top 40 in muGWAS **Significant in muGWAS**

Significant in ssGWAS ⇩

CGEM$_{P923}$

s6	s1	Othr	Mbrn	PI/EC	MPK	Ncls
6.70					PRKCQ	
6.26			TRPM3			
6.20	6.20					BUB3
6.02				SCARB2		
6.00	5.57		FGFR2			
5.95	4.89				POLR1A	
5.89			GNG7			
5.86			VWA3B			
5.85			SYK			
5.81					MSL3	
5.79			CALN1			
5.58				ATP8B1		
5.49					TCF15	
5.48	4.65			LPPR1		
5.44	4.63		HAS2			
5.42					NUP54	
5.38	4.46		BRCAT49			
5.38			KCND3			
5.37			MDGA1			
5.36				SYT17		
5.30				SYNJ2		
5.22					MACROD2	
5.14			SHANK2			
5.13	4.24		AK5			
5.12			LYZL1			
5.09	4.95		MMRN1			
5.08					CTNNBL1	
5.06					SAMHD1	
5.06				MEGF11		
5.04				NLRP4		
5.03					DMRTB1	
5.02					ZMAT4	
5.00			ALPP			
4.99				ABCA1		
4.98					SCMH1	
4.98			LPHN3			
4.97					HNF1B	
4.97					SMARCAL1	
4.95	4.81		BRCAT54			
4.94				AGPAT4		
4.94					ZBTB20	
4.52	4.47		PTCD3			
4.89	4.47		BMPR1B			
4.29	4.29				FBXO38	
4.86	4.24			PARK2		
4.21	4.21			ANO4		
4.24	4.19		ABO			
4.97	4.18			DGKQ		
4.28	4.19		DAP			
4.59	4.11			STXBP1		
4.49	4.07		MRGPRE			
4.82	4.06		NTSR1			
4.04	4.04		MRPL35			

EPIC$_{P427}$

s6	s1	Othr	Mbrn	PI/EC	MPK	Ncls
8.58	5.42					SOHLH2
6.59	4.73			AGPAT3		
6.51	4.11					CELF2
6.48	4.56					STARD13
6.37			PCSK5			
6.33	4.68		mirLET7B			
6.26	4.87			ATP8A1		
6.13	5.66					CHD3
5.88	4.19			TNS1		
5.85	4.36					TRAPPC9
5.82	4.34					CDKAL1
5.6			TAS2R1			
5.50			TMEM132C/D			
5.49	4.05					SIX2
5.40					GLB1	
5.35	4.13		SPATA19			
5.33					ASTN2	
5.27					CHMP7	
5.26						PRKCQ
5.24						E2F3
5.23			NEFL/M			
5.21						NCCRP1
5.21					FLT3	
5.16					EPHB1	
5.15	4.12		CFAP36			
5.14	4.08				GRIA1	
5.13					RASD2	
5.08			COL3A1			
5.08						RARB
5.06			SLC43A3			
5.05					VAV3	
5.05						HMGXB4
5.04			VWC2L			
5.03	4.32					PRKAG2
5.02						LZTS1
5.00			LARGE			
5.00			LSMD1			
4.98			IGSF9B			
4.93			ACAN			
4.90			FKBP1A	SDCBP2		
4.88			KPNA3			
4.77	4.77		OR52K2			
4.64	4.26		GPHN			
4.83	4.24		BMP7			
4.22	4.22					RAPGEF4
3.68	4.20		NFRSF10A			
4.20	4.20		MICAL2			
3.90	4.18					SFRS8
3.57	4.16		PNOC			
4.81	4.06		USP44			

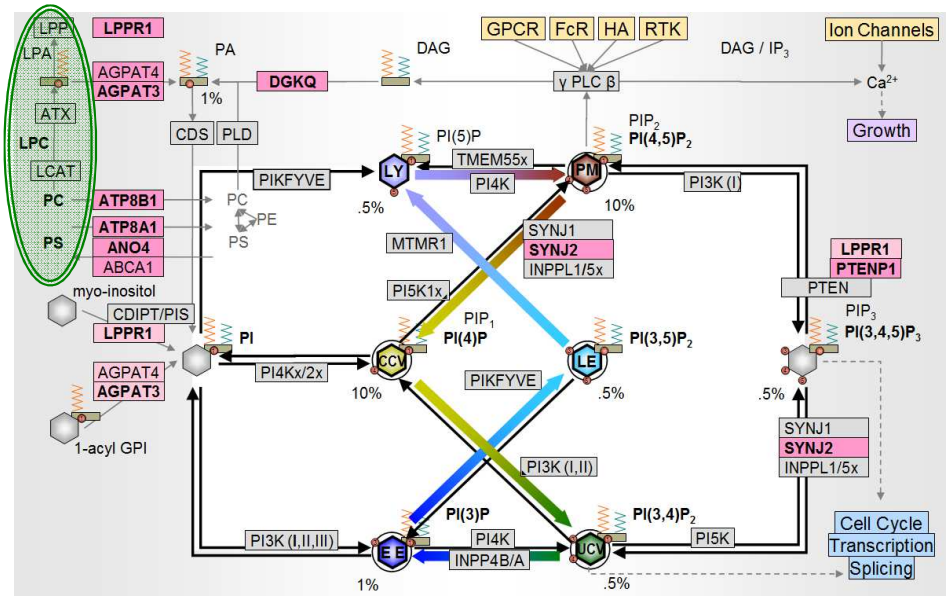
PBCS$_{PB02}$

s6	s1	Othr	Mbrn	PI/EC	MPK	Ncls
7.74	5.83		DOCK8			
6.63						NCOR2
6.59	4.95		CACNA1C			
6.39	4.07			MEGF11		
6.22	4.82		GPC6			
6.14				PTENP1		
6.06	4.60		CDH4			
6.05			CLLU1			
5.97	5.80		RGS3			
5.70			TMCC3			
5.63			SSTR4			
5.43			EDN1			
5.39						ANAPC13
5.35	4.86			TRPC3		
5.34	4.15		COL11A1			
5.33			PRH1			
5.32	4.27			EEA1		
5.22	4.46					RBM23
5.22	4.13		HAPLN3			
5.21	5.08		PTPRG			
5.21			RNASE11			
5.17	4.42			ANXA4		
5.14			CADM2			
5.13	4.39					CDK18
5.12			SLC13A3			
5.11			KIF25			
5.07			MMD2			
5.05			TRIM36			
5.05						PAX2
5.02						GLIS2
5.02			CYB5RL			
5.00	3.83					ISM1
4.99	4.45		BCL10			
4.98	4.19		ZNF98			
4.98						ZFAT
4.95			SDK1			
4.95	4.29		TRMT11			
4.92						HDAC4
4.91						MDFI
4.91						TFAP2A
4.91			HLA-C			
4.61	4.48					FHIT
4.91	4.41			UNC13C		
4.42	4.41		CHIT1			
4.38	4.38		SYNDIG1			
4.74	4.28		SLC25A26			
4.84	4.14			RAB32		
4.12	4.12					A2BP1
4.59	4.07			N4BP3		

Genes Involved in Endo-/Exocytosis identified in BC, PD, and AD

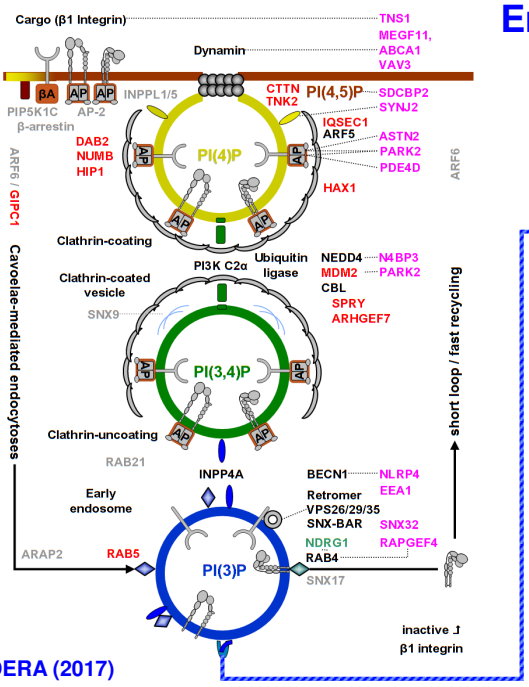
Gene	Function	EEC Function	BC	PD	AD/DLB
ATP8A1	Increasing extracellular PC and PS	(Farge 1999;	(Sjöblom 2006;		(Soderberg 1992)
ATP8B1	enhances endocytosis	Levano 2009;	da Costa 2012)		
		Levano 2012)			
ANO4	Ca+ dependent PL scramblase	(Picollo 2015)			(Sherva 2014)
ABCA1	Regulates cellular lipid efflux;	(Hamon 2006)	(Schimanski 2010;	(Dong 2015;	(Koldamova 2014;
	interacts with *MEGF10*		Zhao 2016)	Pinho 2016)	Pahnke 2014;
					Nordestgaard 2015;
					Boehm-Cagan 2016)
AGPAT3	converts lysophosphatidylinositol	(Bradley 2015)	(Sahay 2015;	(Cheng 2011)	(Sherva 2011)
AGPAT4	(LPI) into phosphatidylinositol (PI)	hsa00564	Hopkins 2016)		
DGKQ	'Regenerates PI from diacylglycerol	hsa00564,	(Filigheddu 2007)	(Lill 2012; Nalls	(Zhu 2016)
	(DAG)	hsa04070		2014)	
LPPR1	complexes with *LPPR3/4/5*,	(Yu 2015)		(Moran 2006)	
	regulates PIS (CDIPT)				

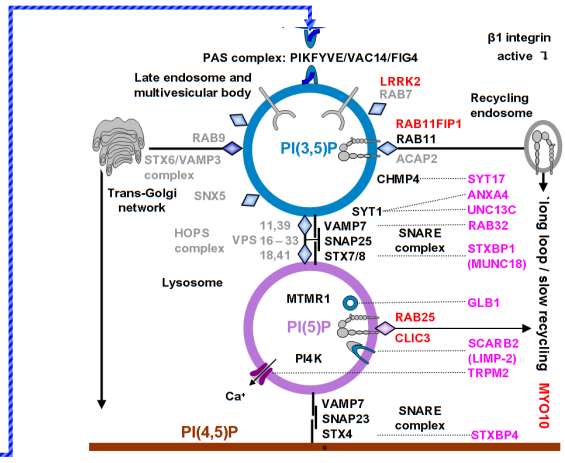
Breast Cancer – Functional relation of the PI/EC genes



PI is synthesized from MI or PA (via CDP-DAG) which can be synthesized from LPA, PC, or PS, or salvaged from IP3 and DAG, it can also be synthesized from 1-acyl GPI.
Genes associated with BC in this GWAS are highlighted in pink (bold: aGWS).
Arrows: PIPs are phosphorylated at a 3-/4-/5-position by PI-kinases (left to right) and hydrolyzed by phosphatases
Colored arrows in the center indicate the sequence of PIs involved in EEC.

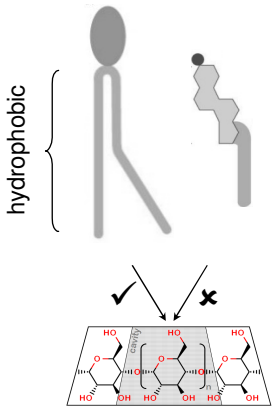
Endo-/exocytosis of β1 Integrin



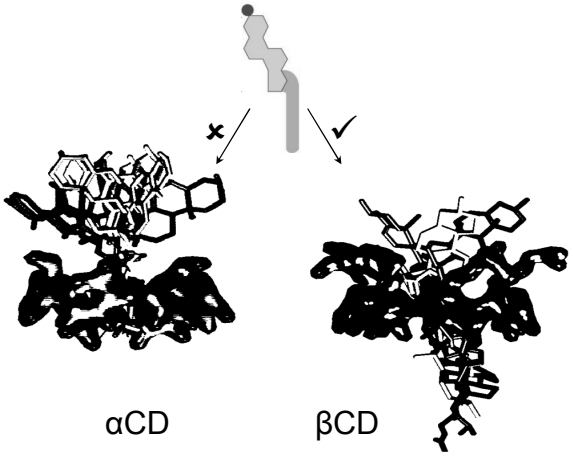


aCD specifrically scavenge PLs

α-Cyclodextrin (αCD)
scavenges Phospholipids ( )
but is too small for Cholesterol ( )
(avoiding the larger βCD's ototoxicity)

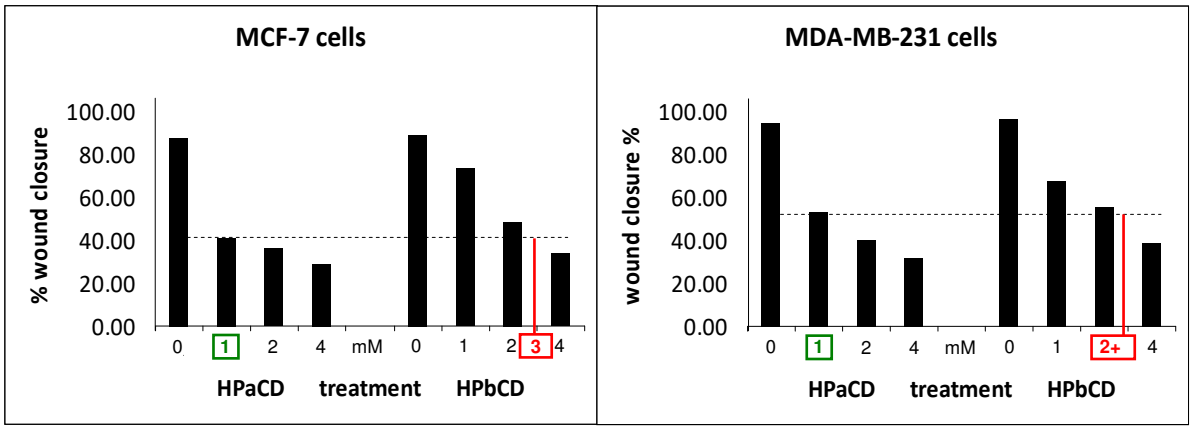


αCD



αCD βCD

Breast Cancer – HPαCD >2x as effective as HPβCD against migration



HPαCD scavenges phospholipids only
Scavenging phospholipids is effective

HPβCD scavenges cholesterol, too
Scavenging cholesterol is ineffective,
causes risk of permanent hearing loss

ASDERA – PI Brochure

1. Epidemiology and impact of Disruption of Active Language Development
2. Data from human genetics, epidemiology, and physiologic studies
3. Proposed pharmaceutical intervention: mefenamic acid (MFA)
4. MFA: Mechanism of action from *in-vitro* and observational studies
5. Preclinical studies of MFA
6. Model systems for the use of MFA to prevent DALD
7. Pediatric use of MFA
8. Prodrugs of MFA
9. Development plan

Text and References viewable as pdf:

Text available below (after FAQs)

ASDERA – Frequently Asked Questions

1. Why do you get GWAS results where others don't ?
2. Has the discovery platform been validated ?
3. What is ASD-002's "Mechanism of Action (MoA)?
4. Was the target walidated (MoA) in animal studies?
5. What is ASD-002's "Proof-of-concept" (PoC) ?
6. Isn't it difficult to diagnose ASD before 24 months?
7. Is 'language regression' age-specific 'mutism' ?
8. Why not just treat the migraines (eg, with triptans)?
9. Isn't it difficult to assess effectiveness?
10. Drug development / management experience ?

ASDERA – FAQ: Why do you get GWAS results where others don't ?

Genetics of Heritable Diseases	If a disease are caused by a single genetic 'letter' variation (SNP), that variation is 'selected against' in just a few generations. Hence, **most heritable diseases are 'epistatic'.** Some variations of SNPs ('words') cause the disease and are selected against, but the individual letters remain in the populations and recombine (no need for *de-novo* mutations).
Limitations of Bioinformatics Tools	Most bioinformatics tools in genetics are based on the statistical methods that were feasible in the 20th century, where memory was scarce. Hence, most GWAS are analyzed one SNP at a time and, thus, can detect only recent (*de novo*) mutations ('letters'), but not the common cis-epistatic risk factors ('words'). Others ignore the sequence of the letters (**rwdo** = **word**).
The ASDERA Discovery Platform	The ASDERA platform is based u-statistics for multivariate data, which were conceived in the 1940s, but never fully developed, because of memory constraints. Only after 2001 (32-bit OS) became it possible to extend u-statistics to incorporate genetic 'grammar' (letter sequence, ...) **to increase power and avoid artifacts** (US 7,664,616).
Result	Where others fail with 100,000s of subjects, ASDERA succeeds with 100s.

ASDERA – FAQ: Has the drug discovery platform been validated ?

Epilepsy	In Childhood Absence Epilepsy, the platform identified all known targets of epilepsy drugs in a sample of 185 cases (compared to publicly available controls) only.(http://www.ncbi.nlm.nih.gov/pubmed/23438886)
Crohn's Disease (CD)	In CD, the platform predicted many of the targets identified in studies of up to 70,000 subjects, in the original 1000 subjects. In addition, the platform identified two more genes involved in fucosylation, suggesting supplement-ing dietary L-fucose as a novel treatment for CD (phase 3 trial in progress).
Breast Cancer	As a finalist of the NCI's U4C breast cancer challenge, the platform identified excessive influx of phospholipids into the PIP cycle as the cause for "derailed endocytosis" and, thus, a drug to regulate supply of phospholipids for the prevention of metastases.(in review, PLOS Genetics)
Phase 2/3	Since the platform can find the "missing heritability" in samples of 100s of subjects only, it can identify genetic risk factors for non-response in phase 3 clinical trials.(confidential)

ASDERA – FAQ: What is ASD-002's "Mechanism of Action" (MoA) ?

Biological model	When neurons are "stressed" (to many signals), they increase the threshold for new action potential to start a signal (hyperpolarize) by exporting potassium (K^+). Loss-of-function in outward K^+ channels causes • epilepsy (ezo-/retigabine) • migraines (Zhang 2013) and • lack-of-language in ASD. (Guglielmi 2015)
Activity	MFA activates outward K^+ channels and inward Cl^- channels. MFA antagonizes inward K^+ channels and outward Cl^- channels.
Efficacy	MFA reduces excitability in rodent and human neurons. MFA prevents induced seizures in rodents.
Effectiveness	(see FAQ: Proof of Concept)

ASDERA – FAQ: Was the target validated (MoA) in animal studies ?

MFA activates outward potassium channels	Fenamates activate outward **K^+ current** in • human *KCNMA1* in jejunum smooth muscle cells [Farrugia 1993, **MFA**/FFA] • pig *KCNMA1* in smooth muscle cells [Ottolia 1994, **MFA**/FFA/NFA; Teramoto 2003, **MFA**] • human *KCNMA1* in embryonic kidney cells [Gribkoff 1996; NFA/FFA] • human corneal epithelial cells [Bockman 1998; FFA] • human *KCNQ2/3* in hamster ovary cells [Peretz 2005, CFA/DCF] • human *KCNT2* in xenopus oocytes [Dai 2010, NFA; Garg 2012, **MFA**...; Thomson 2015] • Guinea-pig *KCNMA1* in vascular smooth muscle cells [Li 2013, FFA/NFA]
MFA prevents induced seizures	MFA reduces neuronal hyperexcitation and, thereby, • PTZ-induced convulsions in rats [Wallenstein 1984] • penicillin-induced seizures in rats [Wallenstein 1987; Ikonomidou-Turski 1988] • PTZ-induced excitation in rats [Wallenstein 1991] • theophylline-induces seizures [Hoffman 1994] • ischemic brain damage in rats [Khansari 2009; Khansari 2012]

ASDERA – FAQ: What is ASD-002's "Proof-of-concept" (PoC) ?

Indication	ASD-002 is **not** for the treatment of **autism spectrum disorders** (ASD). It prevents **migraines** in infants developing ASD. Preventing childhood migraines prevents **lack-of-language**. Note: Infants cannot report migraines, so they cannot be treated (triptans).
Model	ASD-002 is to prevent migraines; hence migraineurs are the "model".
MFA in the treatment of Migraines	Hall (1968): MFA ~ ergotamine/caffein, three attacks per drug Peatfield (1983): MFA > APAP, three attacks per drug
MFA in the prevention of Migraines	Johnson (1986): MFA $>_{ns}$ propranolol > placebo, one month per drug Al-Waili (2000): MFA > placebo, one menstrual period per drug
Summary	MFA is at least as effective as other drugs in treating/preventing migraines. ASD-002 has the same active moiety as MFA.

ASDERA – FAQ: Isn't it difficult to diagnose ASD before 24 months?

Indication	ASD-002 is **not** for the treatment of **autism spectrum disorders** (ASD). It treats **migrianes** to prevent **DALD** in children developing autism. After ASD-002 has prevented DALD, children will still develop ASD, but they will be verbal (have "Asperger's")
Precedent	Mutism is to autism what pneumonia is to the common cold: • we can't treat the common cold / **autism**, but • we can treat pneumonia / **mutism**.
Risk Detection	At 9–12 months, we cannot have a formal diagnosis of **autism**, but we can see risk factors for **mutism** in routine tests covered by CMS: • "red flags" in the routine parentel questionnaire for developmental delay • epileptiform discharges in night-time EEG (at home) • prodromal signs of avoidance of social contacts in eye-tracking.
Prediction	Of the 25,000 children treated every year, >21,000 will develop ASD, >13,500 would become non-verbal (conservative estimates)

ASDERA – FAQ: Is 'language regression' age-specific 'mutism' ?

ICD F94.0 Selective mutism	A persistent failure to speak **in certain social situations** (i.e., school) where speaking is expected, despite speaking in other situations. Applicable to: Elective mutism Can be used together with F84.0 Autistic disorder
Age > 2.5 yr	Selective mutism is typically diagnosed at 2.6–4.1 years of age, when children start to **speak in a social context**.[Viana 2009] "Genetic vulnerabilities" / "Maladaptive reinforcement patterns" Like "dysphasic speech disturbances" in migraines, SM is reversible.
Age < 1.5 yr	At <15 months, children **don't understand social context** (stranger fear). They (s)elect not to speak to humans (but may speak to animals?). K^+ channels as genetic risk / Maladaptive response to migraines EM causes DALD which, like amblyopia (lazy eye), is not reversible.
Hypothesis	"Language regression" is an age-specific form of "(S)elective mutism"[F94.0]

ASDERA – FAQ: Why not just treat the migraines (eg with triptans) ?

Indication	Infants cannot report having migraines. Childhood migraines equivalents have atypical symptoms: • infantile colic, cyclic vomiting, abdominal migraines, • ocular/retinal/convusional migraine, Alice in Wonderland syndrome • paroxysmal vertigo / torticollis
Abortive Drugs	Treatments (abortive therapies): • ibuprofen, acetaminophen, naproxen have been tried • triptans are approved for children >6 years, 1/wk
Preventive Drugs	Treatments (maintenance/prevention): • triptans not suitable (≤1/wk to prevent overuse headache) • valproic acid/gabapentin have been tried • CHAMP trial (8–17 yr) amitriptyline/topiramate/pacebo) aborted for futility
ASD-002 Benefit	MFA (the active moiety) • prevents migraines by targeting the ion channels involved in mutism, • is (UK) approved for chronic treatment in children from 6 months of age.

ASDERA – FAQ: Isn't it difficult to assess effectiveness ?

Indication	ASD-002 is **not** for the treatment of **autism spectrum disorders** (ASD). It treats **migrianes** to prevent **mutism** in children developing autism. After ASD-002 has prevented mutism, children will still develop ASD, but they will be verbal (have "Asperger's")
Outcome	The primary outcome is • ***not*** a measure of autism, • but the number of words spoken at 24 months.
Precedent I	In 2009, Autism Speaks sponsored a study on the effectiveness of Augmentative Communication (AAC).[NCT01013545] The primary outcome was "**Number of words spoken** spontaneously during language sample".
Precedent II	In 2005, Accorda sponsored two phase 3 studies on the effectiveness of dalfampridine (Ampyra®), a potassium channel blocker for the treatment of patients with Multiple Sclerosis. The primary outcome was not a measure of MS, but "**Timed 25 Foot Walk**".

ASDERA – FAQ: Drug development / management experience ?

Drug development experience	ASD-002 is an ester-prodrug of an approved small molecule (MFA). An ester-prodrug is not a new chemical entity (NCE). The prodrug will be produced by Regis, NJ. ASD-002 is not a NCE, but a New Clinical Indication (NCI).
Clinical trial experience	The ASDERA team as broad experience in designing clinical trials. • John Jay Gargus, MD PhD: Pediatrics, Drug Discovery • Knut M. Wittkowski, PhD ScD: Clinical trial design • G. Gold-von-Simson, MD MSc: Pediatrics, Clinical research • Bert Spilker, PhD MD: sold Orphan Medical to Jazz, $122M • Camargo, Services: 505(b)(2) approval pathway • inVentive Health, CRO: Clinical trial services
Full-time management team	The clinical trial for the NCI (not a NCE) will be outsourced to a CRO. inVentiv Health Clinical will lead FDA interactions from pre-IND to NDA and will assume all management responsibilities during the trial.
CEO	TBD in consultation with investors

Translating Results from Human Genetics into a Treatment for Preventing Disruption of Active Language Development (DALD) in Infants with Signs of Maladaptation to Neuronal Hyperexcitability

KNUT M. WITTKOWSKI

For details, see: http://www.nature.com/articles/sp2013124 [1]

1. Epidemiology and impact of Disruption of Active Language Development

Prevalence: Idiopathic forms of autism spectrum disorders (autism, F84.0$_{ICD-10}$, Asperger's, F84.5) include a broad range of neurodevelopmental phenotypes characterized by "persistent deficits in social communication and interactions [as well as] restricted/repetitive behavior/interests/activities".[2] The prevalence of ASD with intellectual disability (ID, IQ<70) due to disruption of active language development (DALD),[3] has been increasing in the US from 1/340 in 2002 to 1/220 (20,000/yr new cases) in 2010.[4] Many more are affected as family members.

Impact: In contrast to animal communications, human language and social interactions date back only 4,000 and 250, rather than millions of, generations, respectively,[5,6] and, thus, are more susceptible to disturbance by environmental factors (stress) than vision, audition, olfaction, and locomotion. Still, lack of language, while not a DSM symptom of autism,[2,7] arguably impacts life (and social skills[8]) more than lack of sight, hearing, smell, or limbs. At a lifetime cost of $10M per case, the benefit of preventing DALD cannot be overstated. Adding loss of productivity, the US financial burden amounts to $1B/d, yet there are no treatments with lasting effects.

Treatments: The two FDA approved ASD drugs, risperidone (Risperdal®) and aripripazole (Abilify®), merely reduce irritability in ≥5 year old (y/o) children.[9] The benefits of behavioral interventions and the (limited) responses to arbaclofen,[10] bumetanide,[11] oxytocin,[12,13] and memantine NCT01972074 were observed (or are evaluated) in higher functioning children only, yet there is little hope for the 20,000/yr US children who become trapped in life-long solitary confinement due to lack of effective verbal and social (VS) communication.[14] The proposed intervention may turn age-specific (s)elective mutism (F94.0$_{DCD-10}$) to be to ASD what pneumonia is to the common cold: more severe, but also more easily treatable than the underlying condition ("Asperger's").

2. Data from human genetic, epidemiologic, and physiologic studies

Genetics of autism: Despite ≈100% concordance in monozygotic twins,[15] >50% heritability among siblings,[16] and a >25% risk for male siblings,[17] the genetics of ASD are still poorly understood.[18] Analyses of two genome-wide association studies (GWAS) by the Autism Genome Project (AGP)[19] had confirmed *CNTNAP2* as a risk factor for neurodevelopmental disorders.[20] Copy number variations were identified in *SHANK2, SYNGAP1*, and *DLGAP2*, yet no "connected pathways" could be postulated from these rare, highly penetrant variations.[21]

Taking advantage of the higher power and specificity of a novel computational biostatistics approach that integrates knowledge about genetics into both the statistical method and the decision criteria (cut-off for significance),[1] we compared non-verbal to verbal cases. We confirmed common genetic risk factors between ***mutism*** and both childhood absence ***epilepsy*** (CAE)[22] and ***migraines***, a triad of channelopathies.[23] More specifically, both studies pointed to epistasis between protein tyrosine phosphatases (PTPRs), which control neuronal growth, and ion channels involved in controlling neuronal hyperexcitation.[24]

Hypothesized etiology of DALD: These human genetics results[1] fit into a unifying hypothesis about the etiology of DALD that is consistent with many established findings in ASD:

- Mutations in growth factor (GF) regulators (PTPRs [1, Fig. 2, 10.00]) cause neuronal overgrowth and early ***enlargement of brain***[25,26] in cases with low IQ[26] or DALD (Figure 1, ASD-REG).[25, Fig. 2, exon in 1 of 116 ASD cases]
- Mutations in potassium/chloride (K^+/Cl^-) ion channels[1, Fig. 2, 2.02e5] cause overexcitation of developing neurons, which then leads to age-dependent forms of ***excitation/inhibition (E/I) imbalance***,[27] in general, and (abdominal) migraines, in particular.[23,28]
- Stressful events (urbanization[29]) may intensify the epistatic interaction between PTPR and K^+/Cl^- genes, consistent with the ***dramatic rise in prevalence*** over two generations.[4]

Migraine, a channelopathy where neuronal hyperexcitability causes hypersensitivity to light and sound, shares epileptiform EEGs with non-verbal autism,[30,31] where a similar gene-gene-environment interaction[32] may cause childhood-specific 'migraines' during the 'stranger fear' period[33] when early toddlers (12–24 mo of age) learn VS skills. Maladaptive behaviors in response to emotional experiences are common in ASD.[34] **Behavioral maladaptation** [1] to avoid migraines may later cause underutilized cortical areas for active language (and, potentially, face recognition/memory)[35] to be permanently pruned (**developmental maladaptation**).

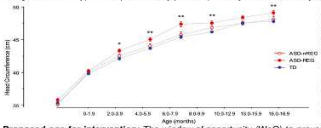


Figure 1: Cross-sectional analysis of head circumference measurements from birth through 18 mo of life. The ASD-REG (regression) group diverges from the ASD-nREG (no regression) and typical development (TD) groups around 4–6 mo of age.[25]

*p< .05, **p< .01

Proposed age for intervention: The window of opportunity (WoO) to prevent DALD is narrow. On the one hand, treatment must succeed before age 24 mo, when synaptogenesis in language-related areas ceases[36] (Figure 3) and the peak periods of (i) synaptic density (Figure 4), (ii) volume increase in the cerebral cortex,[37] and (iii) experience-dependent refinement of cortical association circuitry[38] end. By 24 mo, typical development (TD) children have acquired >400 words and begin to form two-word phrases (Figure 2). On the other hand, symptoms justifying a pharmaceutical intervention cannot reliably be detected before the 9 mo well child exam (from a parental questionnaire (e.g. ITC),[39,40] EEG, and eye-tracking[41] were the critical period of phonetic perception nears its end[42] and social withdrawal (avoidance of eye contact) may already have begun to impair development of language and face recognition.[14,43,44]

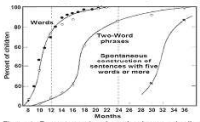


Figure 2: Emergence of various developmental milestones in the acquisition of language.
- 49 Austrian, ○ 114 British, ▪ 500 American children

(adopted from [36] after Lenneberg, 1967, Fig. 4.1)

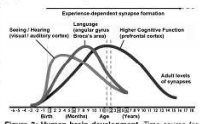


Figure 3: Human brain development. Time course for synaptogenesis. Boxed time points correspond to Figure 4. (modified from Nelson 2000)[36]

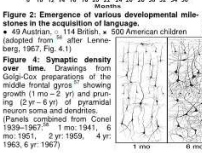


Figure 4: Synaptic density over time. Drawings from Golgi-Cox preparations of the middle frontal gyrus[37] showing growth (1 mo – 2 yr) and pruning (2 yr – 6 yr) of pyramidal neuron soma and dendrites. (Panels combined from Conel 1939–1967:[38] 1 mo: 1941; 6 mo: 1951, 2 yr: 1959, 4 yr: 1963, 6 yr: 1967)

The 2[nd] year of life as the WoO is supported by observations in ASD and related conditions:

- ***Language Regression***, increased ***repetitive behaviors***,[59,60] and a beginning decline of ***fMRI activity*** in language-sensitive cortical regions,[61] of can be seen from ~12 mo of age.[62]
- "***Patches of disorganization***"[63,64] were seen in the brains of >2 yr old children.
- Romanian orphans showed clinical features of "***quasi-autism***" at 4 yr[65] (unless placed in foster care before 24 mo), despite an equal sex ratio and normal head circumference.[66]
- Children receiving cochlear implants still ***develop ID*** unless treated before 24 mo.[67]

In summary, the critical period for preventing maladaptive response to stress involving VS skills is limited. Just as deprivation during a critical period of visual development causes irreversible amblyopia,[68] social deprivation during the 2[nd] year of life – whether externally or internally derived – may impair VS development.[69] At 24 mo of age either the WoO is missed or regression has been averted, so that treatments targeting specific sub-phenotypes can be started,[70] including behavioral interventions and drugs in current clinical trials with older children.

3. Proposed pharmaceutical intervention: mefenamic acid (MFA)

In principle, one could compensate for PTPRs not dephosphorylating GF receptors by blocking them with drugs like Gleevec® (imatinib). Without a definitive diagnosis,[71] however, interfering with growth may be unacceptable even in toddlers at high risk of developing ID. Ion channels, instead, have been targeted in toddlers chronically, e.g., to prevent seizures.[71,72]

MFA was introduced in 1963 as a non-steroidal anti-inflammatory drug (NSAID) and is approved in the UK for chronic treatment of juvenile arthritis from 6 mo of age.[73] It is FDA-approved for acute pain in adults and for dysmenorrhea (including menstrually related migraines (MRM) with poor response to analgesics).[74] In the US, the structurally and functionally similar meclofenamic acid (CFA) is approved for symptomatic relief in arthritis (without formal age restriction).

A controlled release form of MFA, with higher t_{max} 75 av.76-78 and lower intestinal irritation, would not treat ASD, but could break the weakest link in the gene-gene-environment-behavior-development interaction during the early 2[nd] yr of life, the critical period for development of VS skills, from causing DALD. With intolerable 'migraine-like' events during the 'stranger fear'[33] period being avoided, toddlers would not feel the need to 'tune out' so that their brain regions for VS skills would be stimulated enough to prevent them from being 'pruned' starting at the 3[rd] yr of life.[60,81] Preventing mutism would also improve social skills[8] and, potentially, repetitive behaviors.[82]

4. MFA: Mechanism of action from *in-vitro* and observational studies

Like 'COX'-NSAIDs, fenamates also reduce prostaglandin synthesis by inhibiting Cyclo-OXygenase via their COOH group,[83] but it has long been speculated that "other mechanisms may contribute to their [...] effects." Indications that these effects "were produced by actions not related to COX inhibition" [45] suggested "possibly central nonprostanoid visceral antinociceptive action."[45] From 1990, fenamates emerged as "powerful activators of large-conductance, K-selective channels" (BK/CaKC)[84] in rabbit corneal epithelium,[57] Seeing the effect on this COX-independent[85,NPA/CFA] "emergency brake"[83] against hyperexcitability, also in human corneal epithelium,[80,FFA] jejunal muscle,[91] and embryonic kidney cells[92], shifted the focus from COX inhibition to "gap-junction blockade"[93].

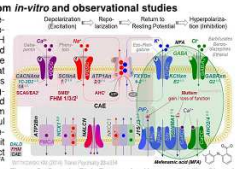


Figure 5: Genetic Risk Factors for Hyperexcitability Shared Among Migraines and DALD. Top: Ions involved in action potential phases. CAE associated genes[22] are highlighted in gray. The three FHM genes also being associated with movement disorders (cerebellar ataxias, SCA6/EA2), severe myoclonic epilepsy in infancy (SMEI), and alternating hemiplegia of childhood (AHC), respectively. Diseases where infant onset is observed.

K^+ channel mutations are known to affect neuronal excitability,[94] causing "channelopathies", such as migraines (including FHM),[95,96] epilepsies,[97] and "channel-ASD".[98] The AGP results[1] implicated *KCNMA1* (AGP 2) and *KCNJ3* (AGP 1) (Figure 5, bottom blue). A recent review highlighted excess intracellular K^+ as a risk factor for mutism.[99] All 5 subjects (and 1 index case) with mutations in these channels were non-verbal: The ***outward*** *KCNMA1* had ***loss-of-function*** variations (a *de novo* 14 bp deletion and A138V) in 2 cases (1[st] intron in the index case and 2[nd] exon in 1 of 116 ASD cases).[99] Out of 52 patients with epilepsy and ID (and 528 controls), 2 twin cases[98] carried ***gain-of-function*** mutations in the ***inward*** *K* channels, *KCNJ2* (K346T)[100] in *cis* with *KCNJ10* (R18Q)[101] and 1 case carried a mutation in *KCNJ10* (V84M).[101]

As with the transient phenotypes of infant CAE and SMEI, where hyperexcitability due to mutations in ion channels and transporters declines as neurons mature, the conditions of hyperexcitability causing DALD are specific to infancy.

5. Preclinical studies of MFA

The efficacy of fenamates to reduce neuronal excitability (MFA being particularly effective) has been shown *in vivo* in numerous animal studies. For instance, MFA pretreatment protects rodents from induced seizures.[102-106] MFA, ibuprofen (IPF), sulindac, and CFA all increase tolerance for chemically induced convulsions.[107] MFA prevents penicillin-induced seizures,[85] attenuates PTZ-induced excitation.[105] MFA, but not IPF, also reduces theophylline-induced seizures.[106] By merely modulating (activating/antagonizing) ASD-related ion channels (VDKCs, irKCs, and CaCCs[107-109]), MFA carries substantially lower risk than anticonvulsants (which block VDCCs or VDSCs), CNS depressants (opening the $GABA_A$ receptor[108]), and bumetanide (blocking *NKCC1* in neonatal brain), see Figure 5. In beagles and rhesus monkeys (even more so than in rats), MFA was the best tolerated fenamate, for up to 2 yr at 100 and 200 mg/kg/d, respectively, 4–8× the UK approved dose for chronic use in infants.[110]

6. Model systems for the use of MFA to prevent DALD

Animal models for DALD: The proposed use of MFA aims to prevent disruption of evolutionarily recent human language development. Yet, in contrast to the evolutionarily conserved excitatory ion channel function in epilepsy and migraines, there is little evidence that innate communication, such as distress calls in mouse pups separated from their dams[110,113] or vocalizations of adolescent male rodents during anogenital sniffing when paired with randomly chosen estrous females[114] fits the paradigm of symbolic language[115] learned in a complex societal context[116] ("cultural transmission"[117]). "There is no [suitable] animal model for human speech and language disorders."[118] Even ants, bees, and birds (who share developmental sensitive periods, *FOXP2* for movement coordination,[119] and *CNTNAP2* for speech production),[119] do not "regress".

Migraines as a model for DALD: In a New Clinical Investigation, humans are typically a better 'model' than animals. While migraine in infants is often "underdiagnosed",[120] because the phenotypes (ICHD[1,6,120]) differ from the typical headaches seen in adults and because many cases resolve before typical phenotypes develop,[122] especially in boys,[123] several "migraine equivalents in childhood"[28] have been identified in autism: infantile colic,[124] cyclic vomiting,[1,6,11,125] abdominal migraines[1,6,12,31-34] and atypical head tilt reflex (torticollis[1,6,8],[126] This clinical evidence is supported by phenotypic, pathologic, epidemic, and genetic evidence: Migraines and DALD share (i) withdrawal from social interactions,[127] (ii) neuronal hyperexcitability in EEG,[128-132] (iii) comorbidity with epilepsy[130-133] and (iv) excitatory genetic variations (Figure 5) confirming lack of language as a channelopathy[23]. Hence, there is no better model to study MFA's effect on DALD than migraineurs in which the causative variations in representative combinations of relevant genetic risk factors have already been 'knocked in' by nature.

[1.6] [childhood] episodic syndromes that may be associated with migraine

[1.6.12] Multiple threads of research [...] have suggested that cyclic vomiting is a condition related to migraine.

[1.6.12] In young children the presence of headache is often overlooked [...] Most children with abdominal migraine will develop migraine headache later in life.

[1.6.2] Onset in the first year. [...] At least one of [...] irritability, malaise, vomiting, ataxia. [...] May evolve into Migraine with aura or cease without further symptoms.

MFA against migraines: The studies of MFA in the human migraine 'model' have already been done. MFA was effective in a double-blind cross-over (DBCO) study (n=24, 18–35 yr, 1 mo).[134] In another DBCO study (3 mo), MFA was as effective as ergotamine/caffeine (which carries a high cardiovascular risk),[135] Over three migraine attacks (n=23), MFA was more effective than APAP.[136] For the prevention of MRM (n=29), MFA was as effective as propranolol.[137] In a meta analysis of interventions against MRM, which have poor response to COX-NSAIDS, MFA 500 mg was the only non-triptan recommended.[74] In the UK, the structurally and functionally similar tolfenamic acid (TFA) is approved for the use in migraines (Clotam Rapid®).

7. Pediatric use of MFA

Acute use: In a controlled study of children age 3–16, MFA had similar antipyretic and higher analgesic efficacy than codeine/phenacetin/ASA. AEs were rare and minor (mostly diarrhea)[138]. Among febrile children age 6 mo – 18 yr MFA (3 mg/kg) was as effective as ASA. No AEs were identified among 71 febrile children (3 mo – 15 yr).[139] MFA (4 mg/kg) was 2.5× more effective than ASA/APAP and similar to that of aminophenazone. The optimal doses in a trial of 87 febrile children (5 mo – 15 yr) were: MFA 4 mg/kg, TFA 0.5 mg/kg, and FFA 1.5 mg/kg (no AEs).[140] Of 50 children (6 mo – 12 yr) with acute respiratory tract infections who received MFA 5 mg/kg for 3–10 d, a single 7 y/o girl had a possibly related AE (enuresis).[141] In total, ~150 children age 3 mo – 3 yr have tolerated MFA well for up to 10 d. From preterm newborns receiving MFA for closure of patent ductus arteriosus (PDA), pharmacokinetics begin to mature within the first weeks of life.[142,143] After rapid absorption from the small intestine, MFA levels peak at t_{max} ≈ 2 h. In the US, MFA is approved for the treatment of pain and dysmenorrhea from 14 yr of age.

Chronic use: Tolerability, dose, and biological activity of MFA in the at risk population are well established. In >20 studies worldwide, ~250 toddlers have tolerated MFA well for up to 10 d.[139-157] Transient convulsions from accidental overdose[158,159] and diarrhea after >2–4 wk of use are the only adverse events (AEs) routinely observed over >50 years in children from 6 mo of age, including chronic treatment of juvenile idiopathic arthritis (JIA).[73] Children with JIA have been treated chronically with MFA in the UK, where the pediatric indication was confirmed in 2012.

Safety records: What sets MFA apart from many other drugs are decades of safety records. In the UK, "Yellow Card" ADR reports over 51 yr did not "identify any evidence [for] potential safety risks".[73] A 2014 custom drug analysis of suspected MFA-related AEs in children age 3 mo – 3 yr by the UK Pharmacovigilance Service yielded only 6 reports since MFA was introduced in 1963.

8. Prodrugs of MFA

MFA adverse events: Although anticonvulsant properties of MFA have been seen in animal studies, MFA can cause seizures in both rats and humans with even moderate overdose.[160,160,161] Like other fenamates, MFA also carries a relatively high risk of causing diarrhea and, with alcohol, smoking, and comorbidities, ulcers.[162] In infants, diarrhea can cause kidney problems from dehydration and children developing autism (especially with "deteriorating" forms),[163] are at a particularly high risk, because they already suffer from a wide variety of gastrointestinal (GI) problems: colics, pain, constipation, vomiting, gastroesophageal reflux (GERD), "leaky gut", gluten intolerance, etc.[164] In addition to having childhood migraines (see Section 6), non-verbal ASD cases, in particular,[165-167] already have a 2–4 fold higher risk of (non-IBD) bowel disorders[168] or diarrhea,[169] making them particularly sensitive to MFA's intestinal side-effects.

Prodrug formulation: To prevent MFA to be acidic in the GI tract, to control the release, and to prolong half-life, MFA will be formulated as a bioreversible ester-prodrug, which consists of two MFA molecules linked via esterification using a bioinactive PEG/disulfide linker that inactivates the acidic carboxyl group until the pro-drug reaches serum (high pH) where it de-esterifies via carboxyl ester hydrolysis to release the parent drug molecules (i.e., a Class IIIB prodrug[170]).

Improved safety and compliance: Compared to the parent drug (MFA), pro-MFA decreases (i) risk of accidental overdose due to rapid resorption in the presence of a narrow therapeutic range,[171] (ii) intestinal disturbances[172] and nephrotoxicity during dehydration from diarrhea,[162] and (iii) inconsistent compliance with frequent dosing.

9. Development plan

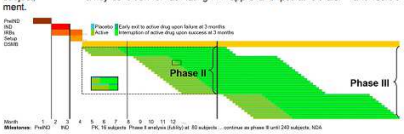
Formulation and dose: As NSAIDs act immediately (in contrast, e.g., to many psychoactive drugs, such as SSRIs), administering pro-MFA with breakfast and lunch only, achieves target daytime MFA serum levels at 50% of the (UK) approved 25 mg/kg/d dose.

505(b)(2) regulatory pathway: An ester prodrug of an approved drug (see propacetamol, an ester of the NSAID acetaminophen) is not a "new chemical entity." FDA, Nov 2, 2016 Hence, a 505(b)(2) application for a (disulfide/PEG) mutual MFA prodrug "may rely on published data and Agency's findings of safety and/or effectiveness for a listed drug."[21 CFR 314.54] The equivalence of preclinical data on activity is available from humans with migraines as a "model system". PK of MFA, dose finding (Phase I), and overall efficacy in other conditions (Phase II) are established from studies of MFA in patent ductus arteriosus (newborns), fever (children), pain/dysmenorrhea /migraines (≥14 yr, FDA approved). Additional safety information comes from the paucity of AE report over >50 years in the UK. This safety information exceeds by far what could be learned from trials of less than hundreds of subjects.

Study population: The open question is whether reducing daytime neuronal excitability in high risk toddlers prevents DALD. 67% (40,000) of 60,000 toddlers developing ASD and 3% (120,000) of 4M TD toddlers per year, show behavioral abnormalities at 9–12 mo.[62] About 60% of the cases (24,000)[62] and only ≈8,000[174] TD toddlers with behavioral abnormalities show epileptiform EEGs as indicators of hyperexcitability. Including only toddlers with abnormal eye-tracking[62] as prodromal signs of behavioral maladaptation[82] and without genetic variants indicating syndromic forms of autism further reduces the population to ≈25,000/yr toddlers (orphan drug request pending). Emerging language tests at 12 mo[47,48] will further improve the predictive value.

In Prader-Willi syndrome, a phase II trial of intranasal oxytocin against poor feeding was conducted in <6 month old children.[175]

Study design: The next step toward the first drug against a severe phenotype associated with ASD is a seamless randomized, double-blind integrated trial in 20 (PK, 1:1) + 60 (Phase II, 3:1, observed for at least 3 months) +160 (Phase III, 3:1, observed for 12 months) healthy toddlers with early symptoms of maladaptation at 9–15 mo of age, starting with individual PK assessments in a crossover to match daytime MFA levels in serum against the parent drug, followed by monthly monitoring of AEs and MFA levels. The primary outcome will be time to mini-sentences and number of words after 12 mo of treatment. After 3 mo, children with sufficient language development can interrupt treatment, but will continue to be monitored for regression, while children lacking progress will be declared 'non-responders' and offered 'early escape' to pro-MFA on a compassionate basis for the trial to "hold out the prospect of direct benefit for the individual subject." [21 CFR 56.102] a key condition for facilitating IRB approval of pediatric trials[8,9,11] and recruitment.



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