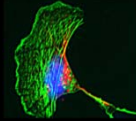


Ibuprofen slows migration of enteric nervous system precursor cells increasing the risk of Hirschsprung-like disease in animal models



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Still nothing to disclose. . .
except that this is work of

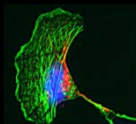


Ellen Merrick Schill

Jonathan Lake
Nandor Nagy
Allan Goldstein
Olga Tusheva
Brittany Graham
Rajarshi Sengupta

Robert Heuckeroth
October 10, 2015

Hypothesis



Hirschsprung disease might be
preventable in some cases

Hirschsprung disease (HSCR)

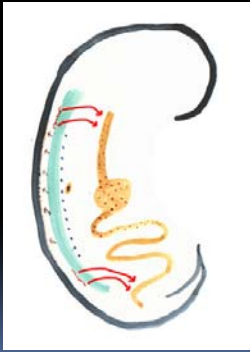
(No neurons in distal bowel)

1:5000 live births
Chronic severe constipation
Growth failure
Bilious emesis
Abdominal distension
Enterocolitis (35%)
Death (3-6%)



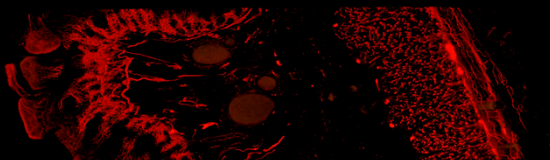
Passarge (2002) Nature
Genetics, 31, 11-12

ENS Morphogenesis

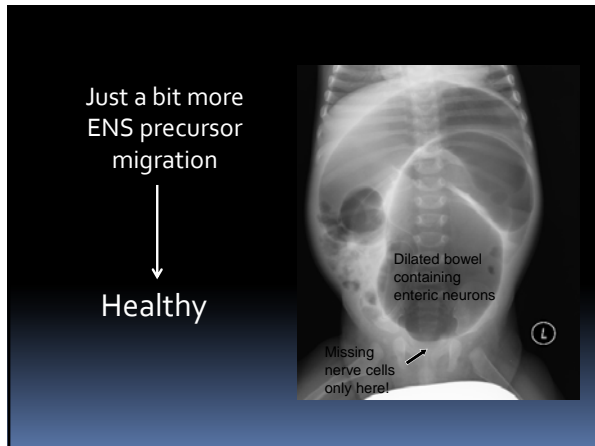


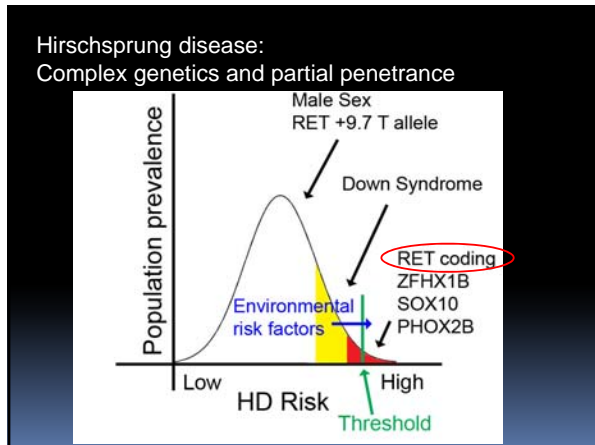
Human bowel neurons and nerve fibers

Fixed tissue; 300 micron section; PGP9.5 staining;
16 stitched confocal images



Rajarshi Sengupta





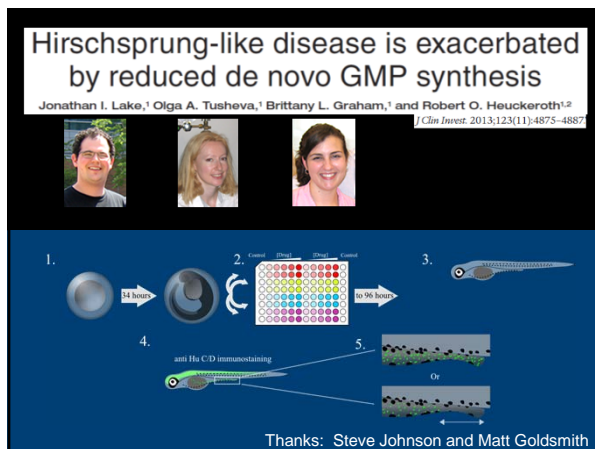
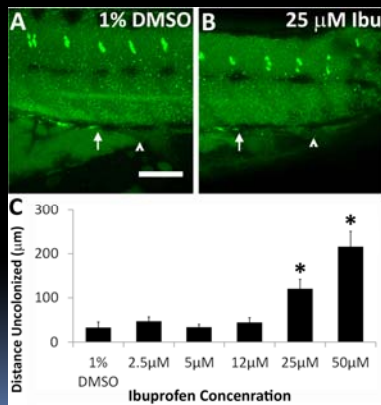


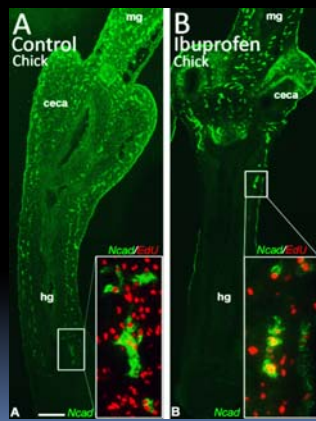
Table 1. Medicines tested for an effect on zebrafish ENS development

Medicine	Human therapeutic blood concentration (μM)	Lowest concentration with an effect (μM)	Concentration range tested (μM)
Acetaminophen	65-130	2,300	330-3,300
Acetylsalicylic Acid	110-1,700	330	55-1,700
Caffeine	10-50	260	5-1,000
Chlorpheniramine	0.013-0.025	260*	13-1,300
Clonidine	0.050*	80*	16-840
Dextromethorphan	0.74-1.3	370	18-1,800
Diphenhydramine	0.034-0.34	100*	15-340
Doxylamine	0.3*	1,300*	130-1,300
Erythromycin	0.68-3.4	>1,400	14-1400
Guafenesin	7.6*	>3,500	250-3,500
Ibuprofen	25-240	25	2.5-50
Loratadine	0.13*	>1,300	65-1,300
Sulfamethoxazole	200-790	2,000	400-7,900

~25% of women use ibuprofen during early pregnancy



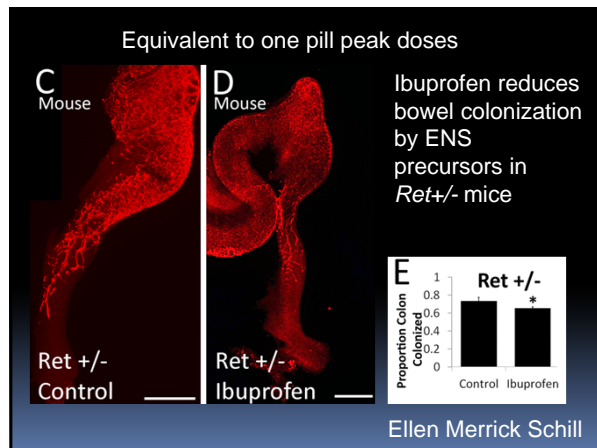
Ibuprofen reduces bowel colonization by ENS precursors in live fish

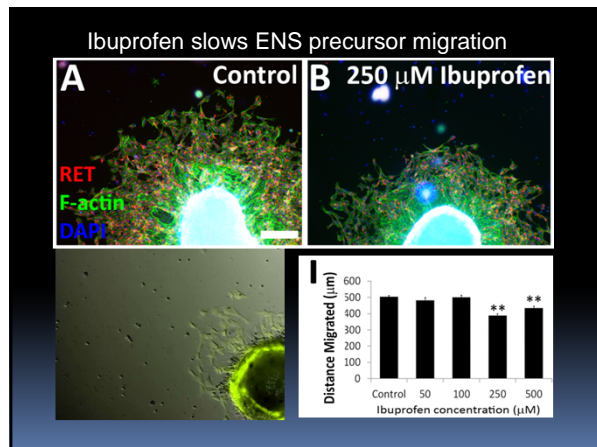


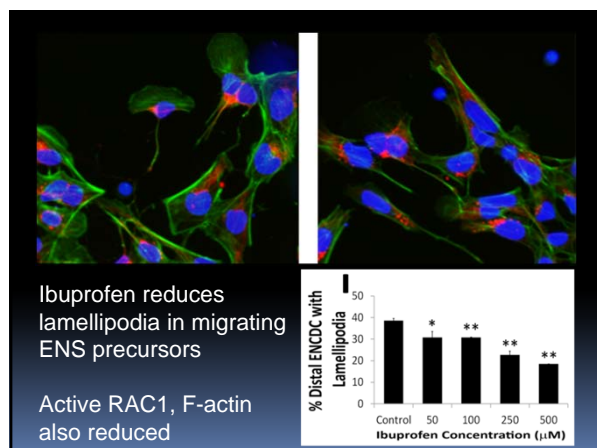
Ibuprofen prevents bowel colonization by ENS precursors in chick

In vitro culture 250 μM

Nandor Nagy
Allan Goldstein







Some cases of Hirschsprung disease may be preventable

Population risk	1:5000
RET heterozygosity	1:2
Down syndrome	1:50-100
Male sex increases risk 4-fold	
1:3125 male	1:12,500 female
Ibuprofen during early pregnancy??	

Heuckeroth Lab

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Beth Maguire
Alisha Jamil
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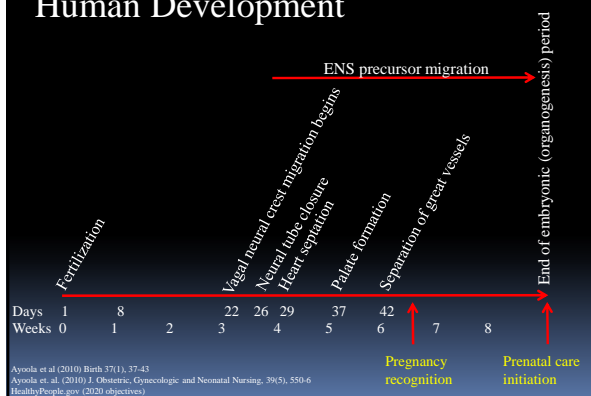
National Institute of Diabetes and Digestive and Kidney Diseases
Burroughs Wellcome Fund Clinical Scientist Award in Translational Research
Children's Discovery Institute of Washington University and St. Louis Children's Hospital
Irma and Norman Braman Endowment for Research in GI Motility Disorders
Suzy and Scott Lustgarten Endowment
The Children's Hospital of Philadelphia Research Institute



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Human Development



All HSCR mutations are partially penetrant

Table 1. Genetic risk for Hirschsprung disease (Sorted by risk factor prevalence in children with HD)

Genetic Risk factor	Gene (NCBI Symbol)	Official	Comments	Relative Risk of HD	Prevalence in children with HD
Male sex		Y-chromosome		2 to 4-fold	80%
Non-syndromic		<i>RET</i> intronic enhancer +9.7 T allele (SNP rs2435357)	T allele present in 25% of Caucasian and 50% of Asian population	5.3-fold TT 2.4-fold TC	60% of affected Caucasians have the T allele
Non-syndromic		<i>RET</i> coding mutation		>2500-fold	50% of familial 20% of sporadic
Down syndrome		Trisomy 21		1800 (approx)	50-fold
Moore-Wilson		<i>ZFX1B</i>	Syndromic	3000-fold	4%
Shah-Waardenburg (WS4)*		<i>EDNRB</i>	Syndromic	5-fold	5%
Other chromosomal anomaly (non-Down)		Deletions, duplications, and translocations		Varies	4%
Shah-Waardenburg (WS4)*		<i>SOX10</i>	Syndromic	~4000-fold	4%
Smith-Lemli-Opitz		<i>DHCR7</i>	Syndromic	50-fold	1%
HCSAS**		<i>L1CAM</i>	Syndromic	40-fold	0.8%
Bardet Biedl		BBS 1-11 (eleven different genes)	Syndromic	30-fold	0.6%
Congenital Central Hypoventilation		<i>PHOX2B</i>	Syndromic	1000-fold	0.5%
Cartilage Hair Hypoplasia		<i>RMRP</i>	Syndromic	25-fold	0.5%
Goldberg-Sprengel		<i>KIAA1279</i>	Syndromic	Unknown	Unknown
Rarely identified mutations		<i>EDN3, ECE1, NRTN, GFRα1</i>	GDNF, 10 cases total reported	Unknown	Unknown
Unknown gene 3p21				4-fold	Common variant
Unknown gene 18q12				5-fold	Common variant
Other loci		9q31, 16q23, 4q31-32		Unknown	Unknown

*WS4 is a manifestation of mutations in several genes listed separately
**Hydrocephalus due to congenital stenosis of the Aqueduct of Sylvius
These data are based on the following manuscripts: (10, 27-32)

