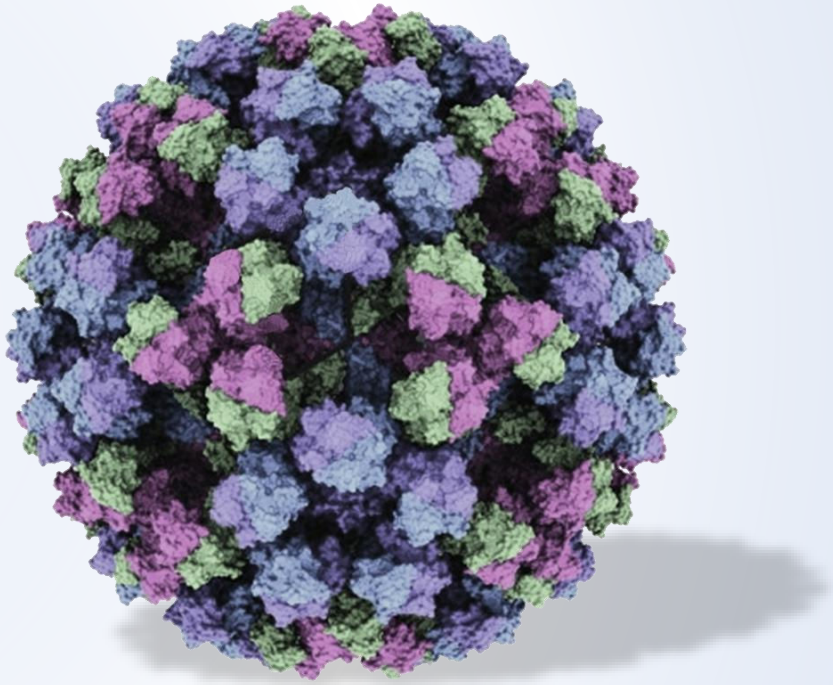
3è Journée Scientifique du Réseau Virus et Greffes
Cité Universitaire Internationale, Paris – January 13, 2025

Norovirus

a persistent acute infection – treatment challenges



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The speaker declares no conflict of interest

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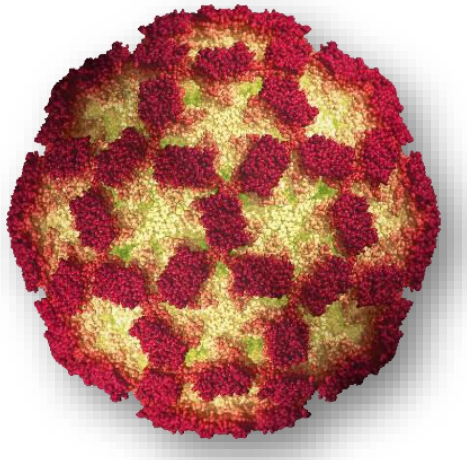
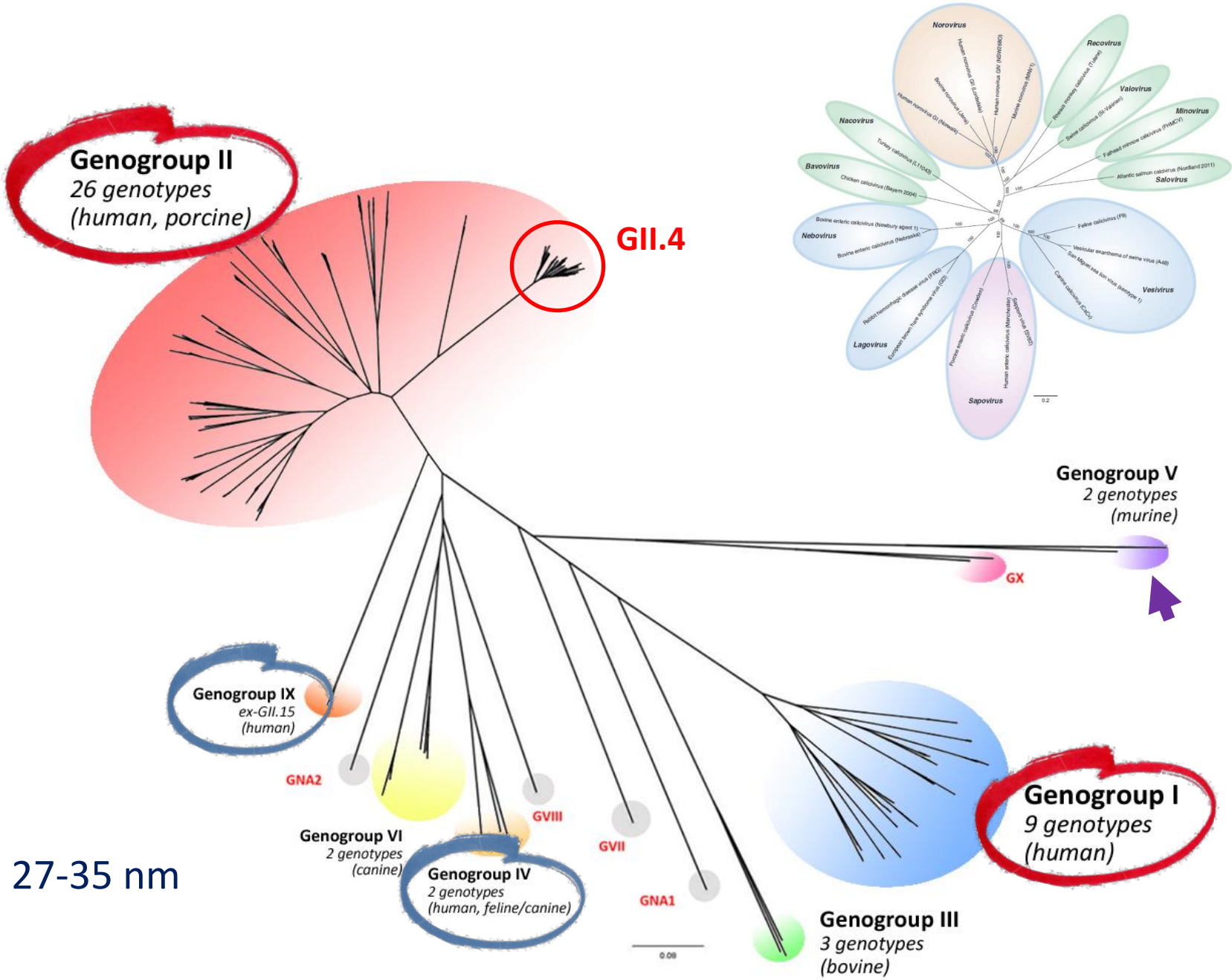
Norovirus

Classification

– ***Caliciviridae* family**
– *Norovirus* genera
– **10+ genogroups**
– human NoVs
= **GI + GII** (+ GIV.1, GIX)



– **small nonenveloped virus** ≈ 27-35 nm
– **ssRNA(+)** ≈ 7,5 kb (3 ORFs)
– **VP1 capsid proteins** = antigens



Chhabra *et al.*, 2019
Fields Virology, Vol. 1, 2021

Epidemiology of norovirus infections

1st cause of epidemic diarrhea in all age groups / 2nd leading cause of traveler's diarrhea

- **85-90% of viral diarrheas** (after ETEC, aka ”turista”)
- 31-87% of nosocomial diarrheas
- 10% community cases seen in general practice

2nd cause of sporadic non-bacterial diarrhea in children <5-yo

- 6-30% of outpatient children ➔ **1st cause if rotavirus vaccination policy**
- 8-15% of hospitalized children for AGE

Disease burden

– number of NoV GE:	**699 million /yr** [489M–1,086B]	➔ 82% in LMIC
– number of deaths:	**219,000 /yr** [171K–277K]	➔ 97% in LMIC
– direct health system cost:	$4.2 billion /yr	
– societal cost:	$60.3 billion /yr	➔ children <5-yo account for 2/3
– productivity losses:	$56.2 billion /yr	

Patel *et al*., 2008; Hall *et al*., 2013; Lindsay *et al*., 2015; Bartsch *et al.* 2016; Harris *et al*., 2019 ; Armah *et al.,* 2023

Characteristics of norovirus outbreaks

Attack rates

– primary:

- grouped case outbreaks: **60%** [23-93%]
- person-to-person: **39%** [31-42%]

– secondary: 4% to 32%

Median duration of an outbreak

= 7 days (1 day to 3 months)

Number of infected subjects

= 2 à 2,000 patients

Norovirus involved in 26% of collective food-borne illnesses (CFBI)

– number of CFBI: 125 million /yr [70M – 251M]
– number of deaths: 35,000 [16-80,000] décès par an
– 59% of clinical CFBI (among all transmitted pathogens)
– 27% of CFBI are due to non-GII.4 NoVs
– 37% of CFBI are due to a mixte infections including GII.4

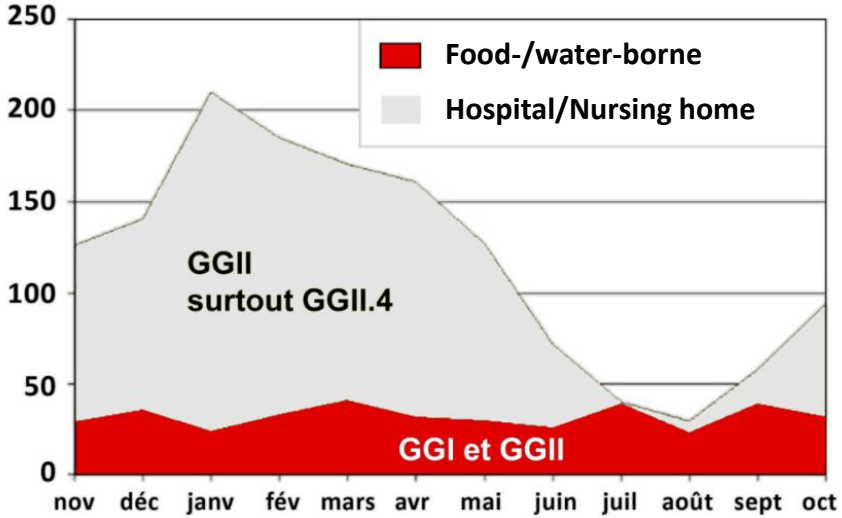
→ **Codex alimentarius**

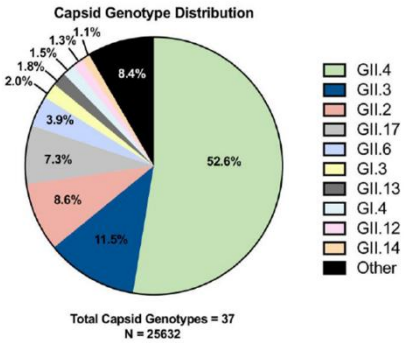
Kaplan *et al.*, 1982; Dolin *et al.*, 1972; Keswick *et al.*, 1985; Seitz *et al.*, 2011; Verhoef *et al.*, 2015; Havelaar *et al.*, 2015

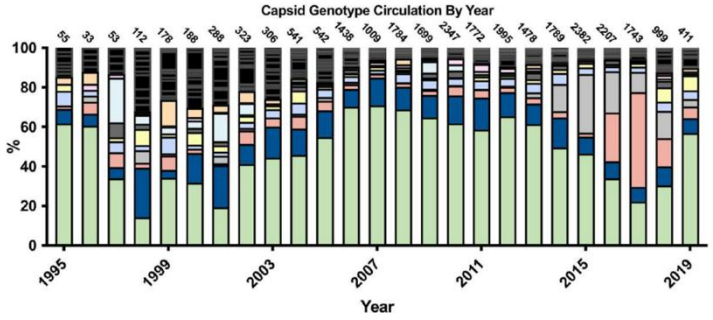
Norovirus genotype epidemiology and seasonality

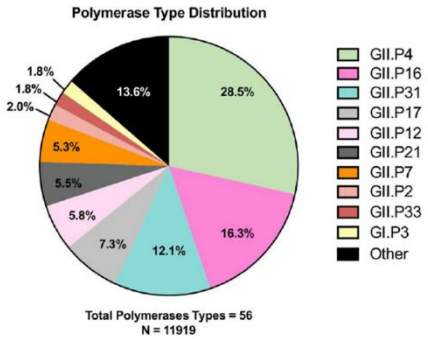
Norovirus infections

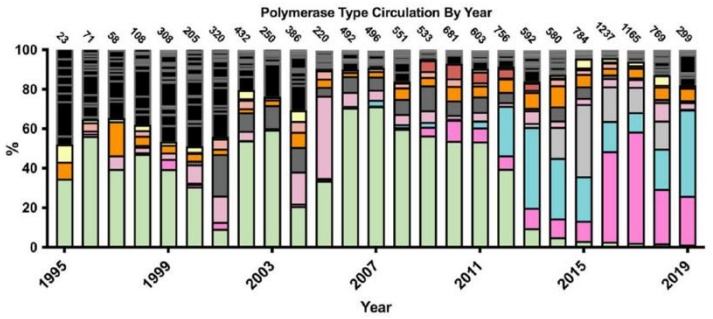
- **sporadic (human-to-human) ≈90%**
  - winter peak: **norovirus GII.4 +++** = 80-90% of cases
  - prevalence = 12-28% in population
- **food-and waterborne outbreaks ≈10%**
  - all year round: GI + GII, all génotypes
  - involved in **26% of all CFBI** (59% of clinical CFBI)

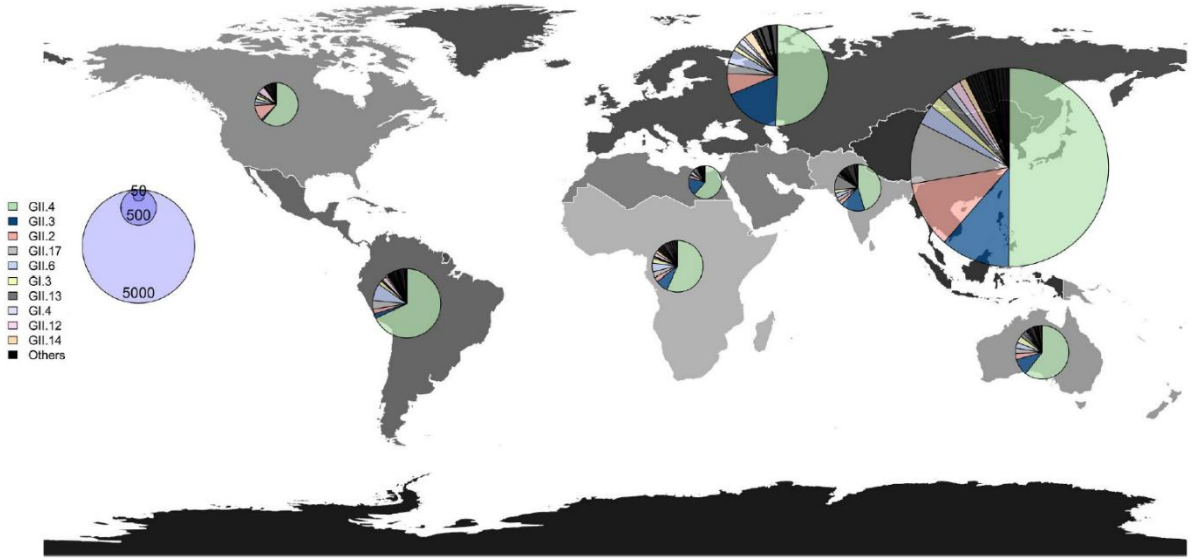






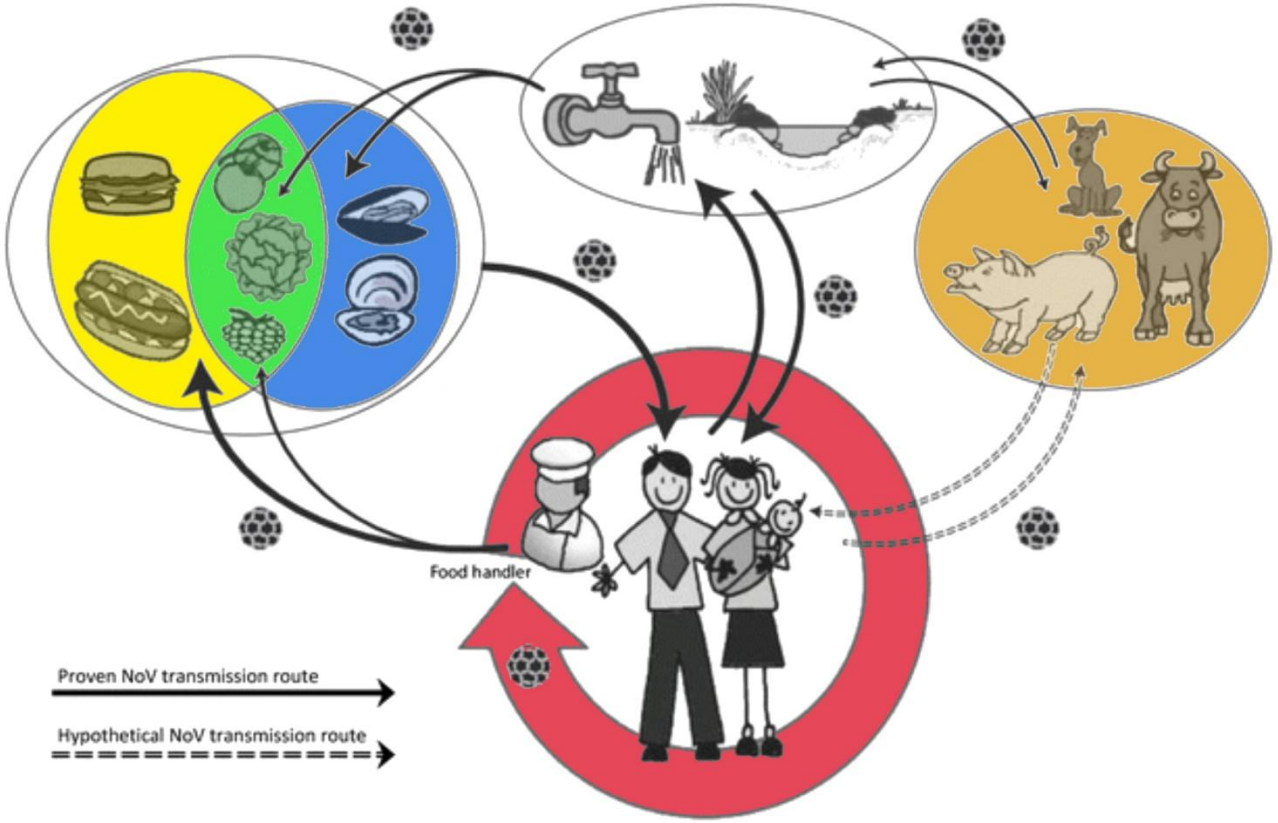






Lopman *et al*. 2003, Kendra *et al.*, 2022

Transmission by fecal oral route



Indirect

environment

food-borne ++

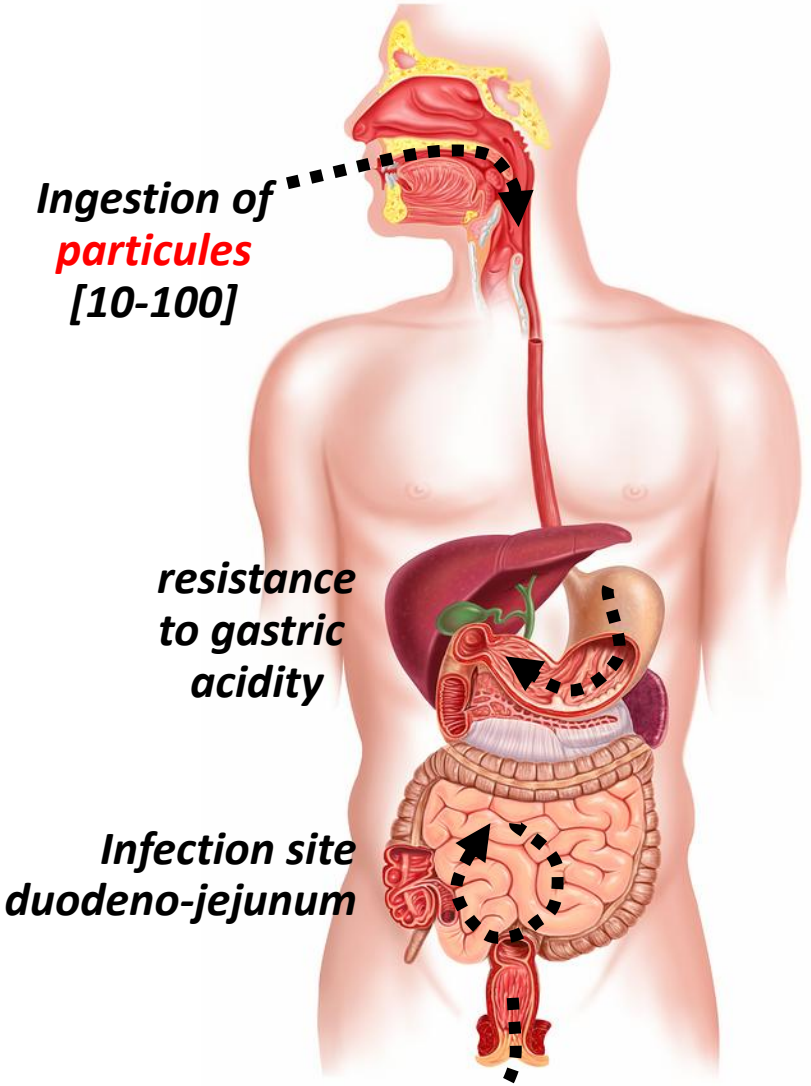
water-borne +

Direct human-to-human

hand-borne +++

contaminated surfaces

airborne (vomit)



Mathijs et al., 2012

Cellular tropism and physiopathology

Viral replication sites

– **enterocytes?** ➔ organoids

– **Tuft cells** = role in chronicity?

Attachment

– **receptor**: unknown (🡐 lipid raft?)

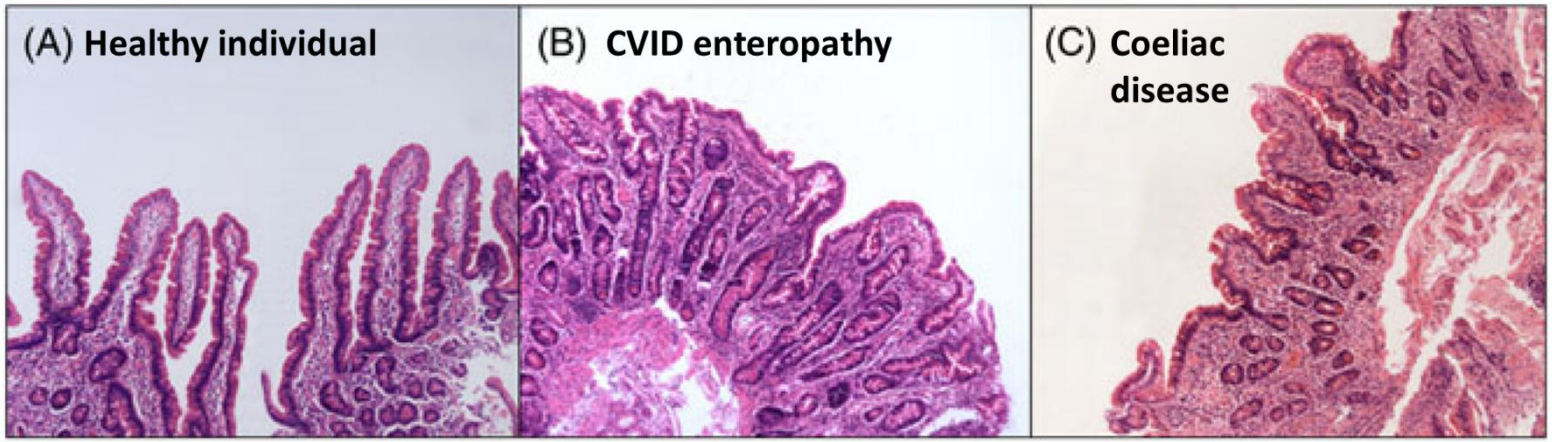
– **ligands: HBGA** ABO / Lewis = saliva and gut

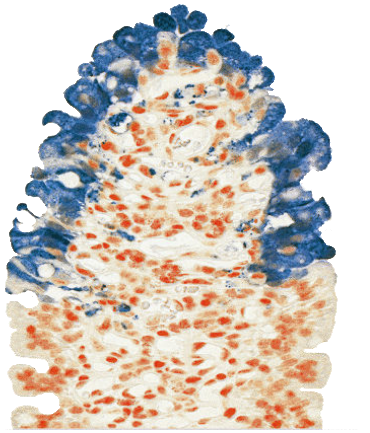
➔ genetic resistances: FUT2 = 20% / FUT3 = 5-30%

Dual mechanism diarrhea *= secretory disorders + epithelial barrier dysfunction*

– brush border alteration: ↗ Cl^- excretion, disturbed enzymatic activity, malabsorption

– disorganization of tight junctions: increased enterocyte apoptosis, water leakage into lumen





Infected villosity

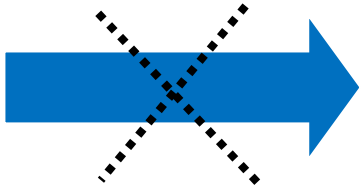
Widerlite *et al.*, 1975; Meerof *et al.*, 1980; Morrotti *et al.*, 2004; Troeger *et al.*, 2009; Brown *et al.*, 2017

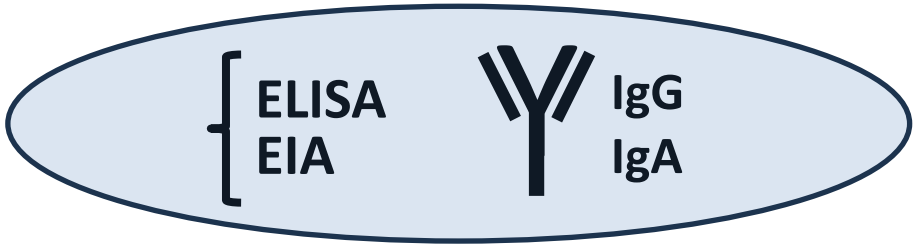
Marionnaud et al., 2001; Lindesmith et la., 2003

Virological diagnosis

INDIRECT DIAGNOSIS

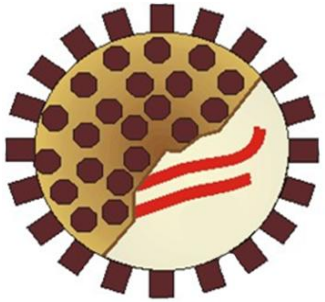
= serology: **antibody detection**



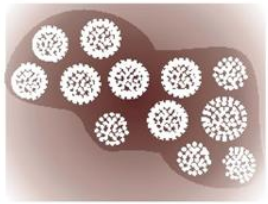


DIRECT DIAGNOSIS

= detection of
- *whole **virions***
- *virus **components***
- *virus **genome***



Viral particles



SEM

Viral culture

Antigens

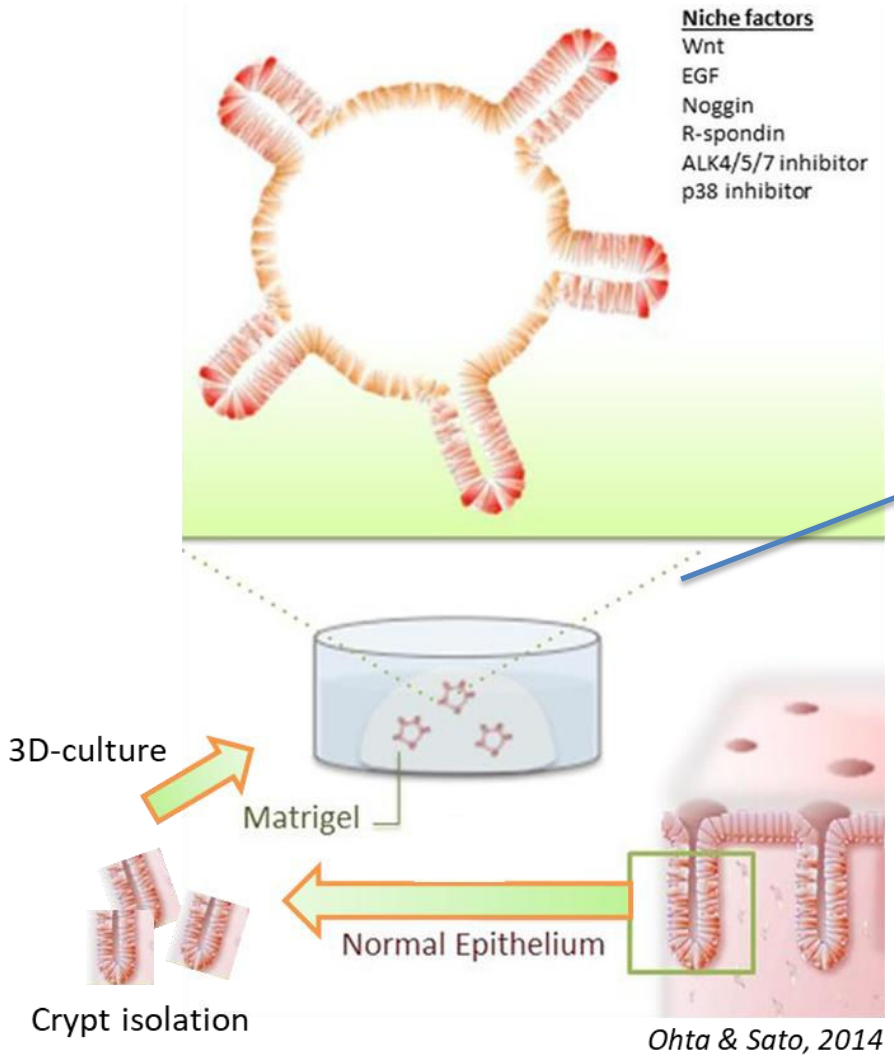
ELISA, EIA
ICT

Viral RNA
(± viral load)

RT-PCR, RT-qPCR

Organoids: human intestinal enteroids (HIE)

3D- and 2D-cultures

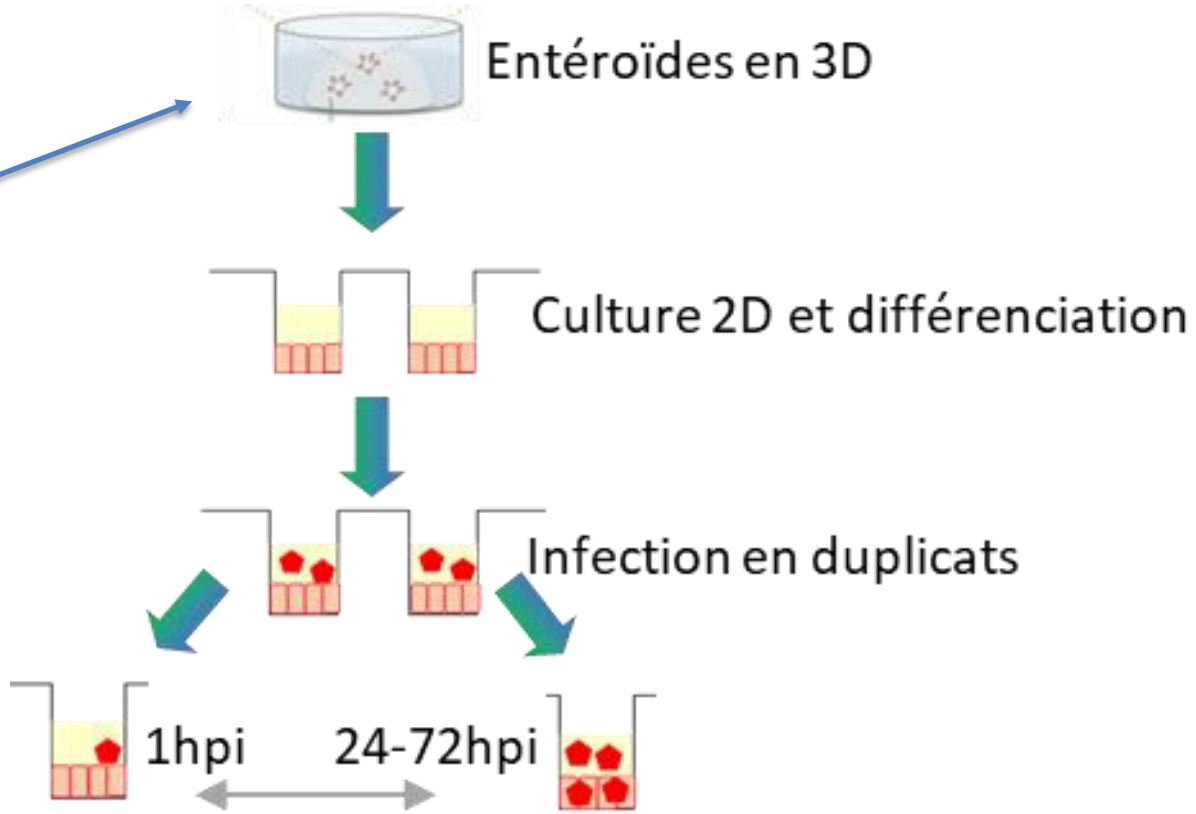


Ohta & Sato, 2014

Science — RESEARCH ARTICLES

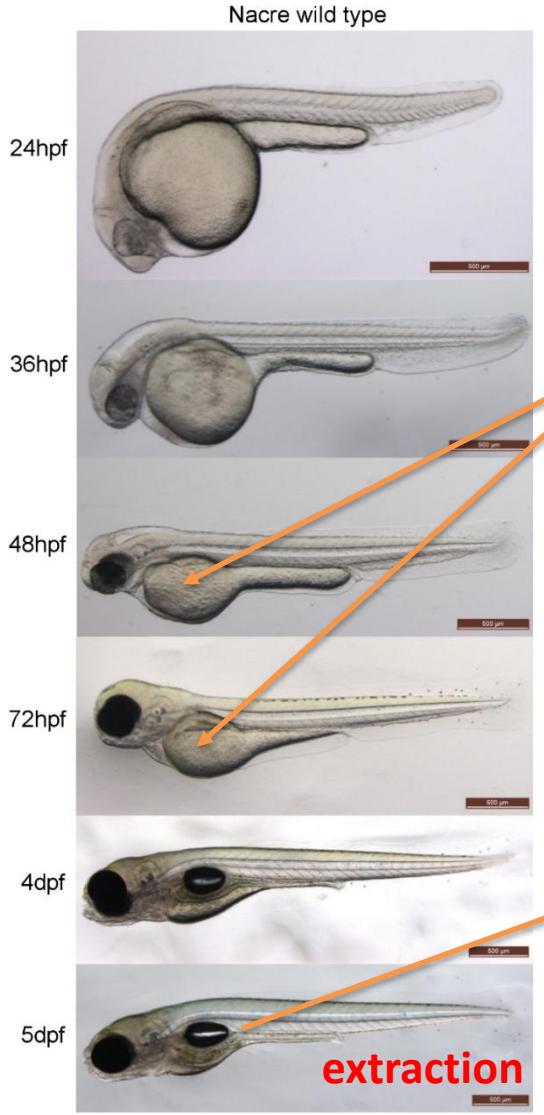
Replication of human noroviruses in stem cell–derived human enteroids

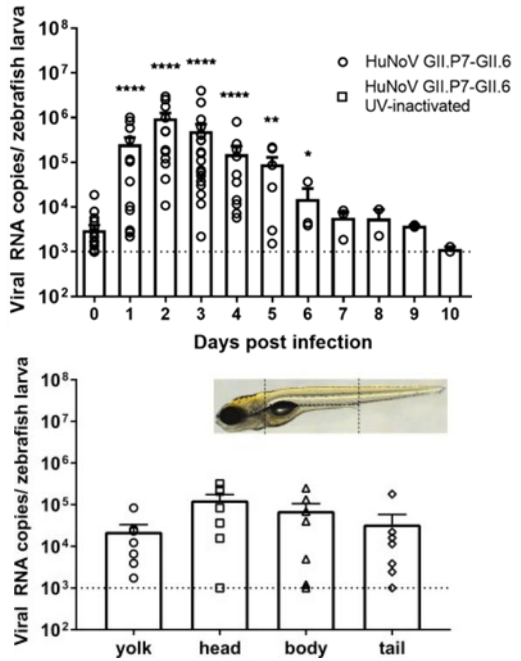
Khalil Ettayebi,[1*] Sue E. Crawford,[1*] Kosuke Murakami,[1*] James R. Broughman,[1] Umesh Karandikar,[1] Victoria R. Tenge,[1] Frederick H. Neill,[1] Sarah E. Blutt,[1] Xi-Lei Zeng,[1] Lin Qu,[1] Baijun Kou,[1] Antone R. Opekun,[2,3,4] Douglas Burrin,[3,4] David Y. Graham,[1,2,5] Sasirekha Ramani,[1] Robert L. Atmar,[1,2] Mary K. Estes[1,2†]



Ettayebi *et al.*, 2016 ; Euller-Nicolas *et al.*, 2023

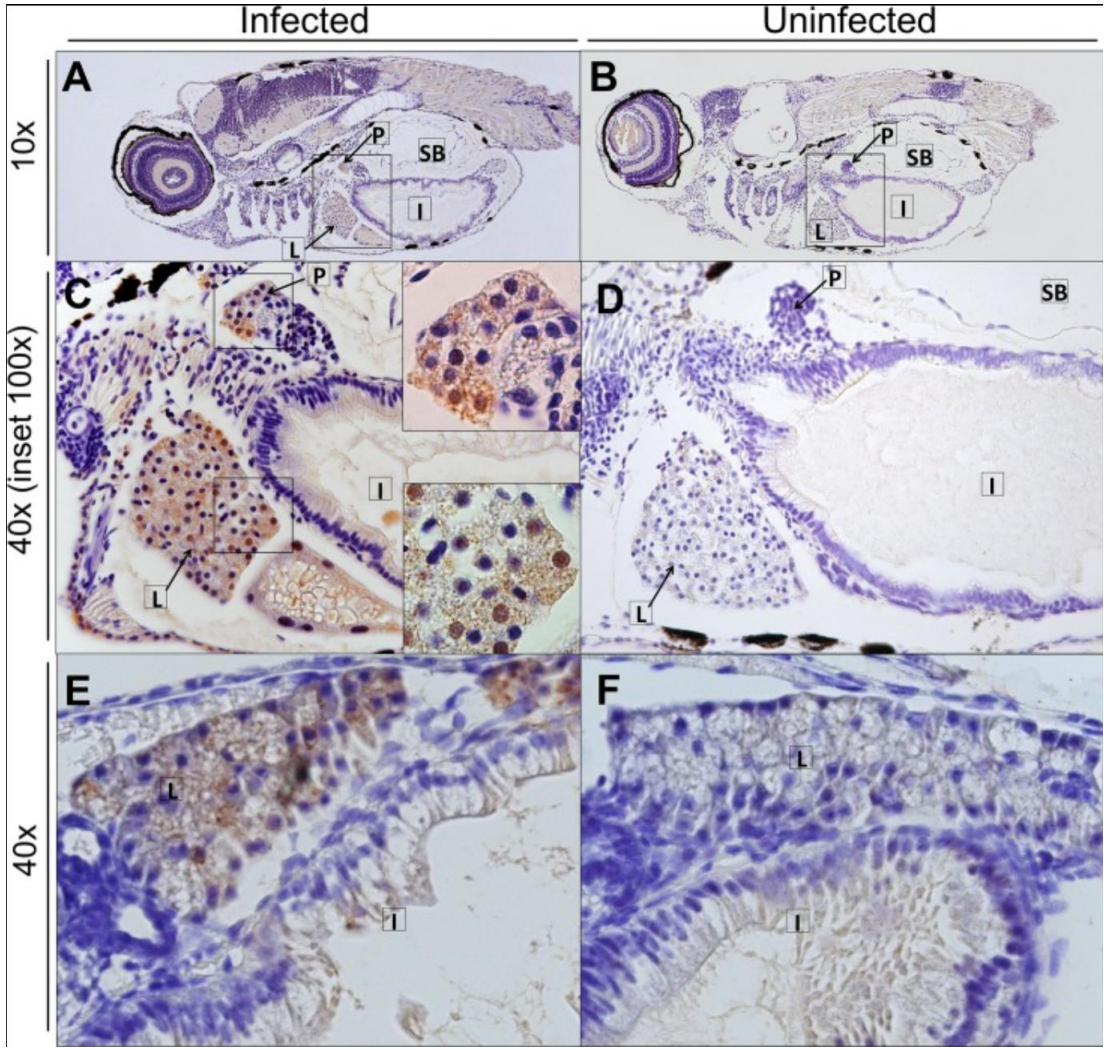
Norovirus culture in Zebra fish larvae





A robust human norovirus replication model in zebrafish larvae

Jana Van Dycke[1], Annelii Ny[2], Nádia Conceição-Neto[3¤], Jan Maes[2], Myra Hosmillo[4], Arno Cuvry[1], Ian Goodfellow[4], Tatiane C. Nogueira[1], Erik Verbeken[5], Jelle Matthijnssens[3], Peter de Witte[2*], Johan Neyts[1,6*], Joana Rocha-Pereira[1*]



Novodvorsky *et al.*, 2015; Van Dycke *et al.*, 2019

Clinical features

Mild acute gastroenteritis

– many pauci- or **asymptomatic cases (30%)**
– tends to be more severe at the extremes of life
= potentially severe **dehydration**

Typical symptoms

nausea	**79%**
vomiting	**69%**
diarrhea	**66%**
fever	37%
chills	32%
abdominal cramps	30%
myalgia	26%
headaches	22%
sore throats	18%

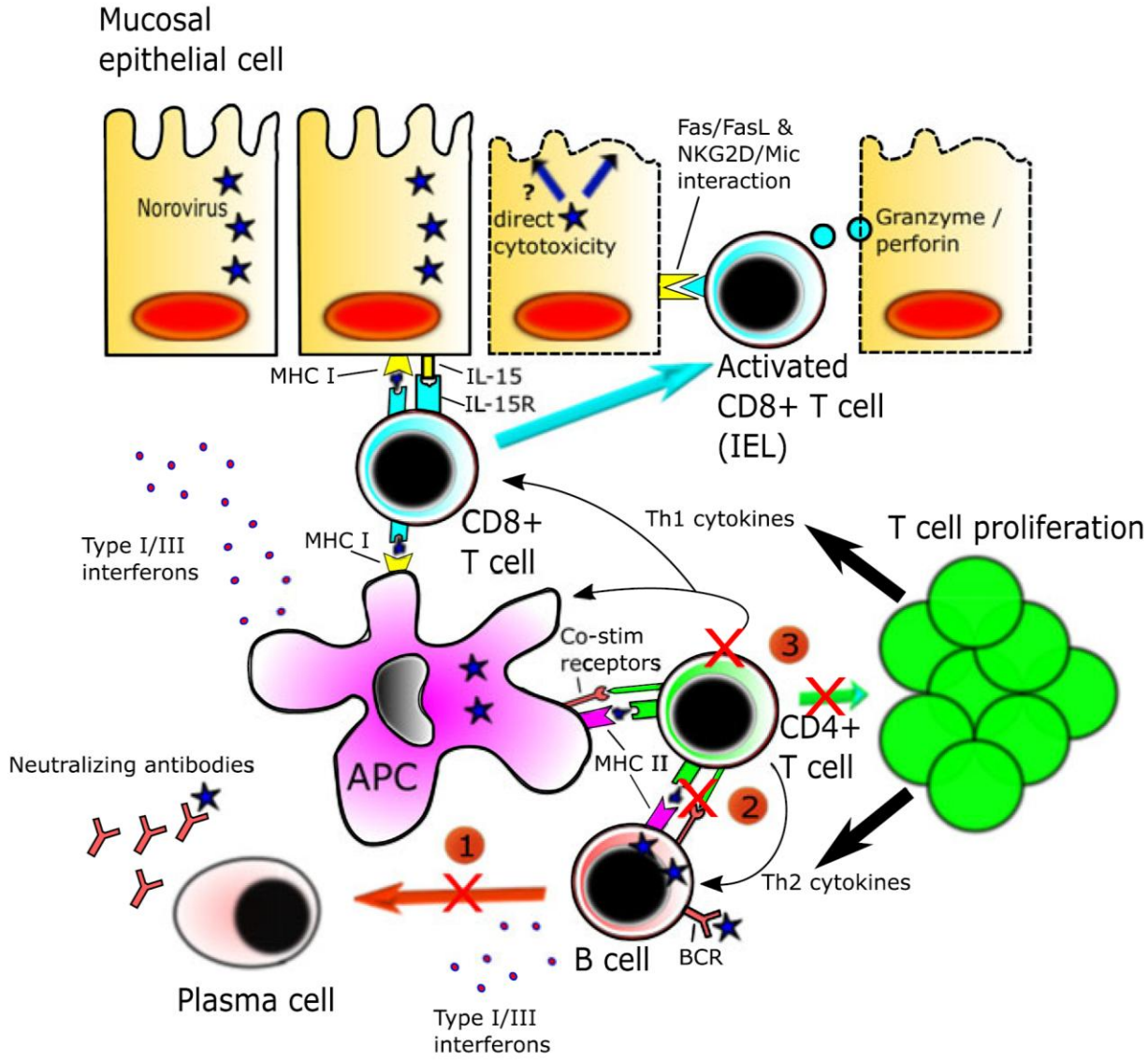
➔ **incubation time = 1-2 days**
symptom duration = 1-3 days
excretion duration = 3-4 weeks

Kaplan et al., 1982

Putative model of the immune response to norovirus

Immune response in immucompetent

- **NoV infects APC, B cells or epithelial cells**
  ➔ direct cytotoxicity + INF types I/III release
- **NoV Ag presentation**
  ➔ MHC-I to CD8+ T cells / MHC-II to CD4+ T cells
- epithelial IL-15 may activate further T cells
- **CD8+ T cells + NK induce apoptosis**
  ➔ granzyme and perforin + Fas/Fas ligand binding
- **CD4+ T cells proliferate and release cytokines**
  ➔ ↗ APC activity, CD8+ T cell cytotoxicity, and B cells/plasmacytes Ab production



Brown *et al.*, 2017; Moral *et al.*, 2022
Winder *et al.*, 2022; Lockhart *et al.*, 2023

Host defense

Adaptive immune response

– **short-term**: from a few months to a few years (same strain) } = expose to **new infections**
homotypic response
➔ serum IgG levels not correlated with resistance to infection

– **local and long-term**: **3 to 9 years** } = **rapid and early response**
related to previous infections ➔ **secretory IgA**

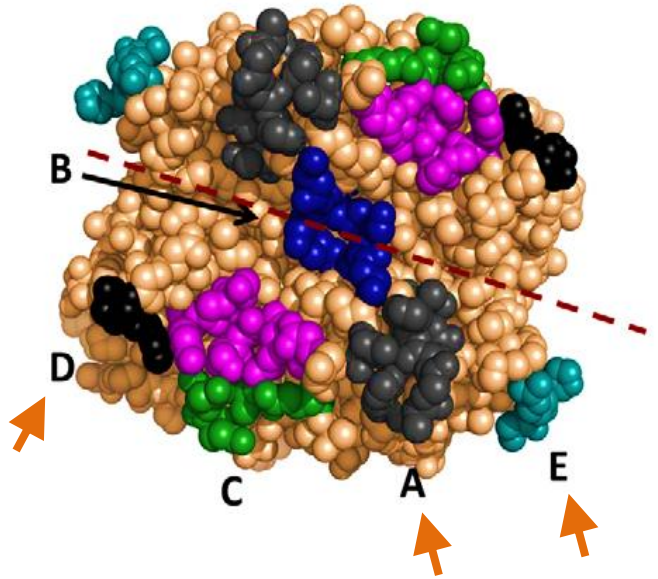
Cellular immune response

– **Th1 type mainly = ↗ IFN-γ, ↗ IL-2**
– **homologous** et **heterologous**
– **CD4⁺ et CD8⁺ T cells required for virus clearance**

Innate immune response

➔ role of TLR, IFN-α…

Antigen sites
(VP1 dimer)



Wyatt *et al*., 1974; Parrino *et al*., 1979; Tacket *et al*., 2003; Lindesmith *et al*., 2005; Siebenga *et al*., 2007; Lindesmith *et al*., 2008; LoBue et al., 2010; Lindesmith *et al*., 2012; Simmons *et al*., 2013; Cannon *et al*., 2019

Chronic norovirus infections in the immunocompromised

Clinical context

– **primary** immunodepression**:** CVID, SCID, agammaglobulinemia…

– **secondary** immunodepression: solid transplants, hematopoietic transplants (HSCT), chemotherapy, HIV…

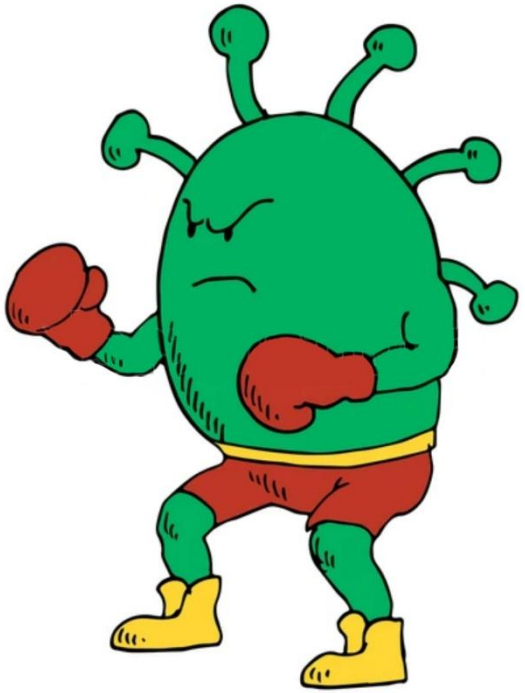
Dysfunction in immune deficiency

– B cell differentiation / plasmocyte Ab production

– T and B cell interactions

– CD4+ T cell cytokine release and proliferation

➔ NoV clearance failure + epithelial damage by CD8+ cytotoxic T cells



Chronic diarrhea

– virus detection: **feces ± blood**

– long duration: **few months to up to 3 years** (likely intermittent)

Infection outcomes

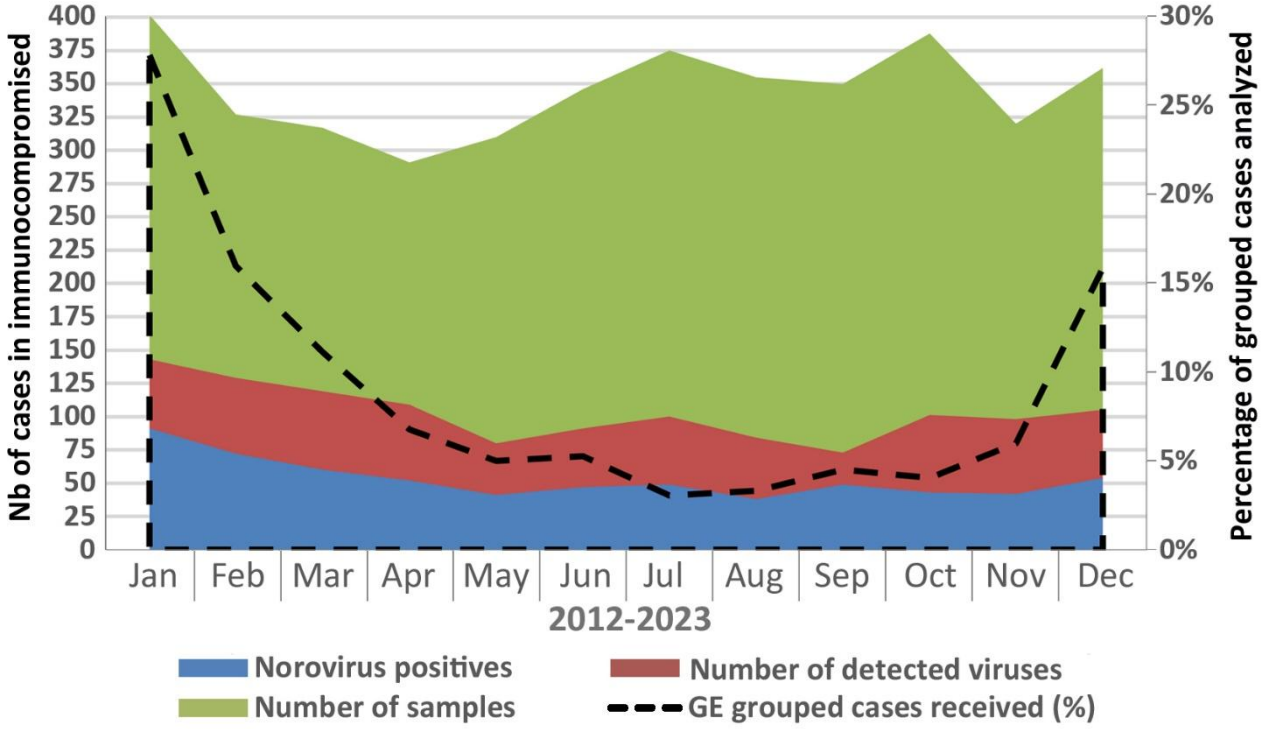
– graft loss, intestinal pneumatosis, dehydration

– degraded quality of life

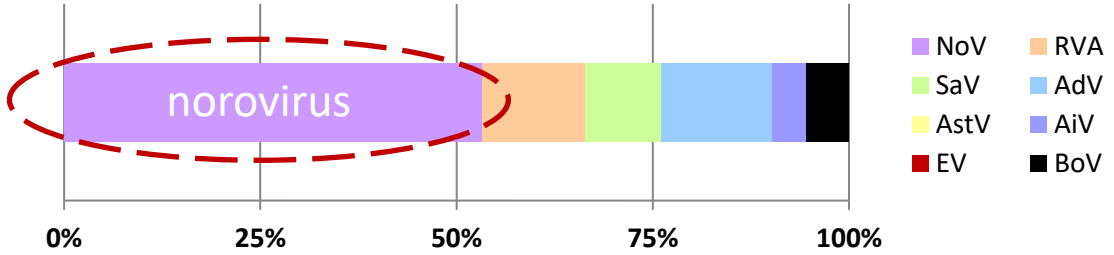
– **death**

Sporadic cases in immunocompromised patients

From 2012 to 2023
4143 samples analyzed



>50% of positive cases are caused by norovirus (95% of GIIs)



1232 (29.7%) positives for 1 virus
638 (51.8%) positives for norovirus

NCRgev annual reports

History of attempts to treat chronic norovirus infections Brown *et al.*, 2017

Lactose-free diet	no effect *(HIV)*	Wingfield (2010)
Gluten-free diet	no effect *(CVID entheropathy)*	Woodward (2015)
Breast milk	no effect *(heart transplants, CVID)*	Nilsson (2003); Van de Ven (2011)
Enteral immunoglobulins	no effect *(heart transplants, CVID)*	Nilsson (2003); Van de Ven (2011); Echenique (2016); Frange (2012)
	decrease in stool frequency	Florescu (2008, 2011); Ebdrup (2011)
	(kidney/pancreas/intestine transplants, CVID, agammaglobulinemia)	
	successful clearance *(lung transplants, CVID)*	Chagla (2013); Gairard-Dory (2014); Duraisingham (2015)
IV immunoglobulins	no effect / few decrease in stool frequency	Nilsson (2003); Wingfield (2010); Van de Ven (2011)
	(heart/pancreas transpl., HIV, CVID, inherited immunodeficiency)	Duraisingham (2015); Echenique (2016)
Interleukin-2 (IL-2)	no effect *(HIV)*	Wingfield (2010)
Nitazoxanide	no effect *(pancreas transplant, CVID, post-HSCT)*	Duraisingham(2015); Echenique (2016)
	successful clearance *(pre- and post-HSCT)*	Siddiq (2011); Morris (2015)
Ribavirin ±IFNα	no effect *(CVID)*	Van de Ven (2011); Duraisingham (2015); Woodward (2015)
	successful clearance *(CVID enteropathy)*	Woodward (2015)
Immunosuppressive drugs	no effect *(allogenic HSCT, CVID enteropathy, CVID)*	Roddie (2009); Van de Ven (2011); Woodward (2015)
	(steroids, anti-TNFα, azathioprine)	
	successful clearance *(heart/lung transplants, post-HCST)*	Boillat Blanco (2011); Engelen (2011)
	(sirolimus, everolimus)	
Antibiotics	no effect *(renal transplant, CVID)*	Roos-Weil (2011); Duraisingham (2015)

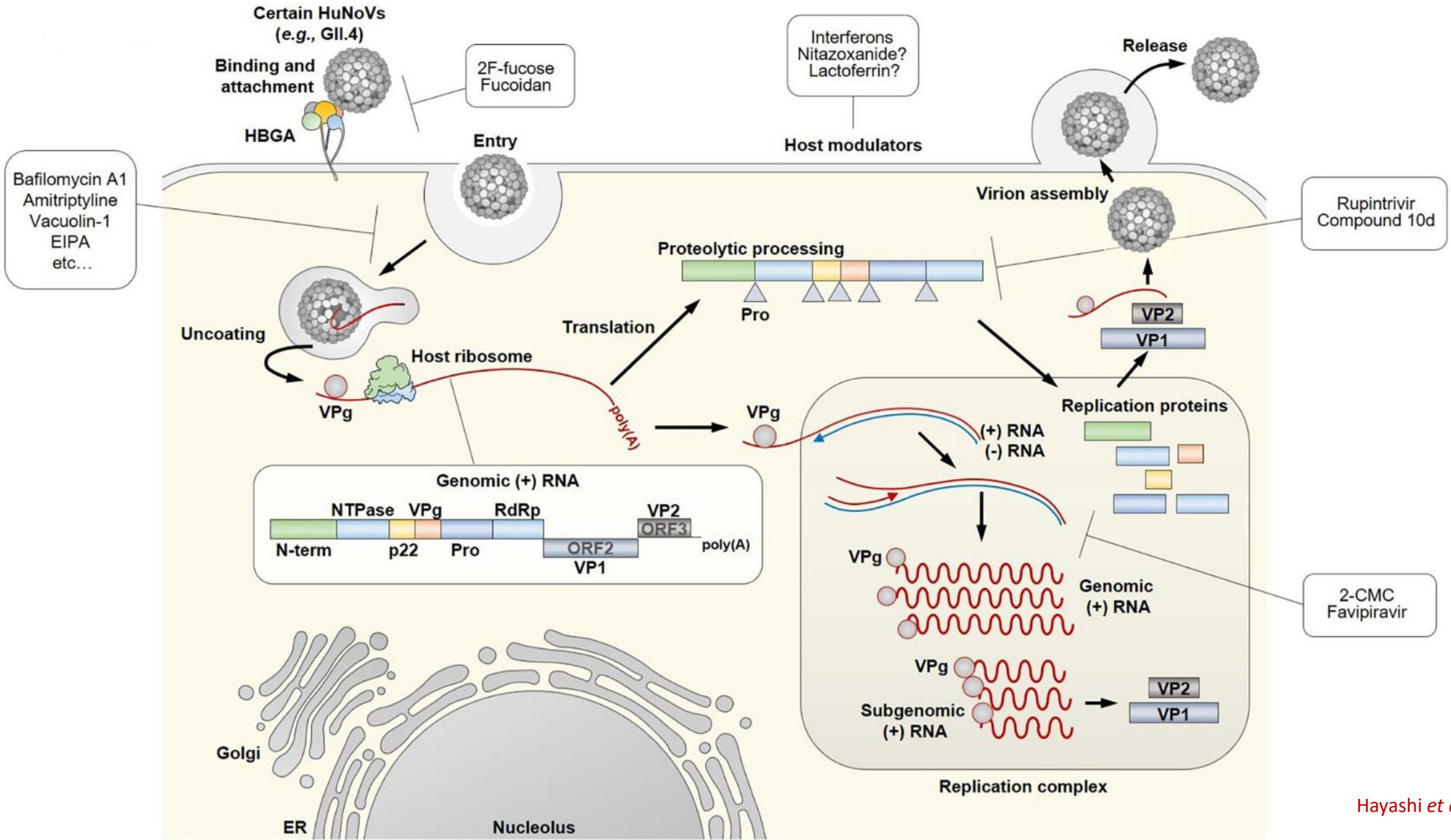
Effective drugs on norovirus replication?

Antiviral Compound	Class of Inhibitor	Stage of Viral Life Cycle	Molecular Target	Mechanism of Action
Citrate	Carbohydrate analogue	Viral entry	Viral capsid	Blocks binding of P domain of viral capsid to HBGAs
Rupintrivir (Lufotrelvir)	Peptidomimetic inhibitor	Translation	Viral protease	Inhibition of NoV 3CLpro blocking the cleavage of NS polyprotein, essential for production of viral progeny
CMX521	Purine nucleoside	Genome replication	RdRp	Direct inhibition of viral RdRp acting as final chain terminator
2CMC	Nucleoside analogue (cytidine)			
7DMA	Nucleoside analogue (adenosine)			
NITD008	Nucleoside analogue (adenosine)			
Favipiravir	Nucleoside analogue (pyrazine)			Direct inhibition of viral RdRp by competition with ATP and GTP at the initiation and elongation steps; Lethal mutagenesis
Ribavirin	Nucleoside analogue (guanosine)			Inhibition of viral RdRp by depletion of intracellular GTP pools
NAF2	Non-nucleoside analogue			Allosteric inhibition of RdRp
Suramin				
PPDS				
NF023				
Resiquimod	TLR agonist	Host factor	TLR7	Stimulation of IFN production by TLR7 agonism
γ-PGA			TLR4	
17-DMAG	-		Hsp90	Inhibition of Hsp90 activity
Nitazoxanide	Thiazolide	Other	Not known	Not known

2CMC—2′-C-methylcytidine; 7DMA—7-deaza-2′-C-methyladenosine; γ-PGA—Poly-γ-glutamic acid; 17-DMAG—17-dimethylaminoethylamino-17-demethoxygeldanamycin; RdRp—RNA dependent-RNA polymerase; TLR—Toll-like receptor; Hsp90—Heat shock protein 90; HGBGAs—Histo-blood group antigens; IFN—Interferon.

Santos-Ferreira et al., 2021

Norovirus drug targets



Hayashi *et al.*, 2024

Nitazoxanide: an effective drug?

Thiazolide: a broad-spectrum antimicrobial

- treatment of parasite-induced gastroenteritis
- rare clinical successes in treating chronic norovirus infection
- **mechanism on noroviruses is unknown** but in:
  - astrovirus: possible induction of IFN response by activation of protein kinase R
  - rotavirus: inhibition of VP7 maturation, hampering viroplasm formation; interference in morphogenesis

Synergetic effects of NTZ in association with ribavirin

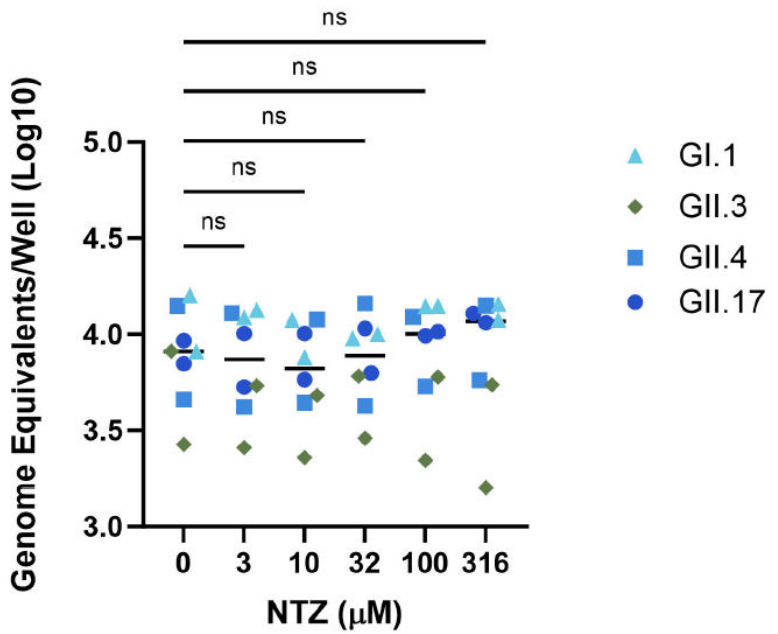
on NoV replicon systems ➔ triggers interferon stimulated genes

BUT no to weak inhibition of replication in jejunal HIEs

at non-cytotoxic concentrations

+ no influence on innate immunity for antiviral activity

May help to reduce diarrheal symptoms in CNI
but NTZ fails to clear norovirus replication…



ALINIA **(nitazoxanide)**

Siddiq *et al.,* 2011; Dang *et al.,* 2018; Santos-Ferreira *et al.,* 2021/2024; Lewis *et al,,* 2024

Ribavirin: a universal viral treatment?

Ribavirin-resistant chronic norovirus infection-associated enteropathy in common variable immunodeficiency. Case report and review of the literature

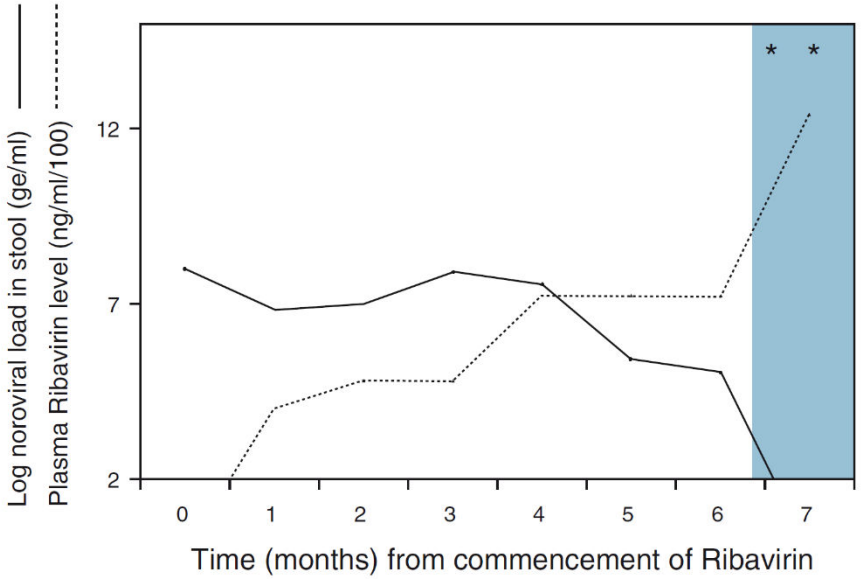
Gonzalo González-Morcillo[a,*], Beatriz Calderón-Hernanz[a], Joaquín Serrano-López de las Hazas[a], Ana Isabel de Hita-Santabaya[b], Joan Riera-Oliver[c]

Antiviral drug with a large spectrum

- nucleotide analogue of guanosine
- active on various RNA/DNA viruses: HCV, HEV, HSV, RSV, PIV, IV, HIV, CMV, AdV, PXV…
- CNI: used alone or in association with other drugs: Igs, NTZ, immunosuppressants…

Few evidence of effectiveness on chronic norovirus infections

- few cases with clinical improvement and virus clearance
- viral clearance (if obtained): several months



Woodward *et al.*, 2015; Gonzalez-Morcillo *et al.*, 2022

Table 1 Summary of clinical reports of patients with chronic norovirus infection and CVID-associated enteropathy treated with ribavirin.

Author	Sex	Age at CVID diagnosis / Age at enteropathy onset	Enteropathy presentation	Intestinal histology	Treatment received against norovirus	Total months of Norovirus infection	Ribavirin dosage	Ribavirin plasma levels	Clinical improvement Virus clearance Muscle tissue restructuring
Van de Ven et al (11)	Male	5/14	Chronic diarrhea Nausea Abdominal pain Weight loss	Duodenal villous atrophy. Lymphocytic infiltration of esophagus, antrum, duodenum, ileum	IVIG Breast milk RBV	24	10-day course	No	No
Duraising-ham et al (12)	Female	14/36	Diarrhea Nausea Anorexia Weight loss	Villous distortion in the terminal ileum with neutrophilic infiltration	IVIG OIG PN RBV	16	400 mg/day 2 weeks	Yes	No
Woodward et al (8)	Male	15/25	Diarrhea Weight loss	Partial villous atrophy	PN IFN RBV	40	800 mg/day 21 months	Yes	No
	Female	29/43	Diarrhea Nausea Weight loss	Sub-total villous atrophy	PN RBV	25	800 mg/day 12 months	Yes 1500 ng/mL	Yes
	Male	30/65	Diarrhea Weight loss	Sub-total villous atrophy	PN RBV	34	800 mg/day 9 months	Yes	Not evaluable (Patient died – lung adenocarcinoma)
	Male	33/44	Diarrhea Nausea Weight loss	Sub-total villous atrophy	EN PN RBV	36	200 mg three times per week/ renal function-adjusted 12 months	Yes	Yes
	Male	42/48	Diarrhea Weight loss	Partial villous atrophy	IFN RBV	46	800 mg/ day 21 months	Yes	No

PN, parenteral nutrition; IFN, alfa interferon; EN, enteral nutrition; IVIG, intravenous immunoglobulin; OIG, oral immunoglobulin; RBV, ribavirin.

Favipiravir: clinical improvement but no viral clearance

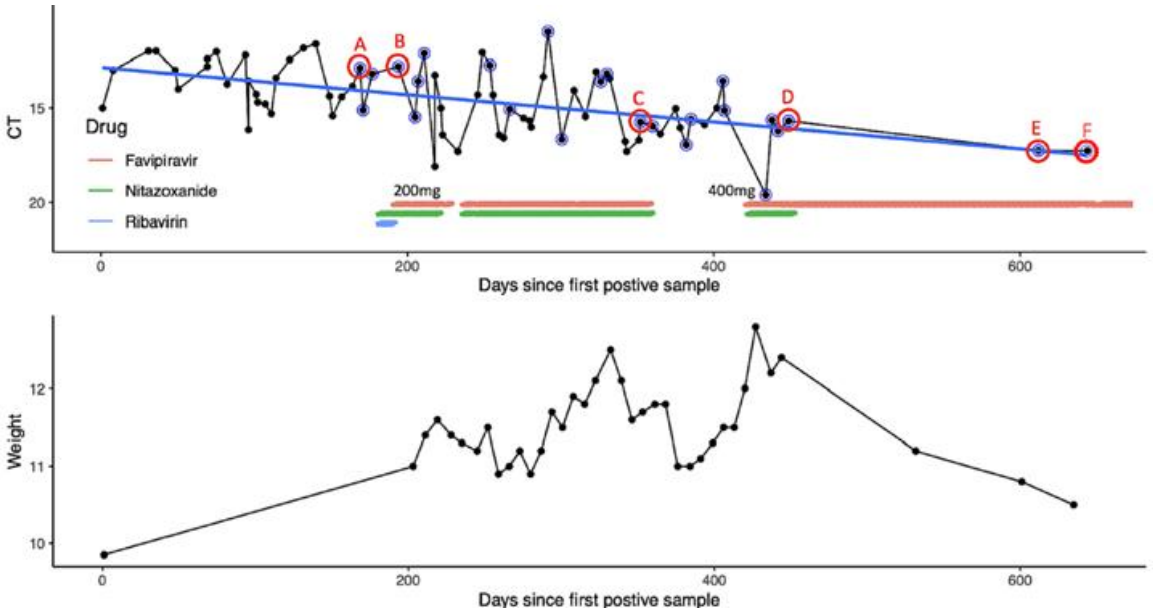
AVIGAN **(favipiravir)**

Pyrazine: nucleoside analogue

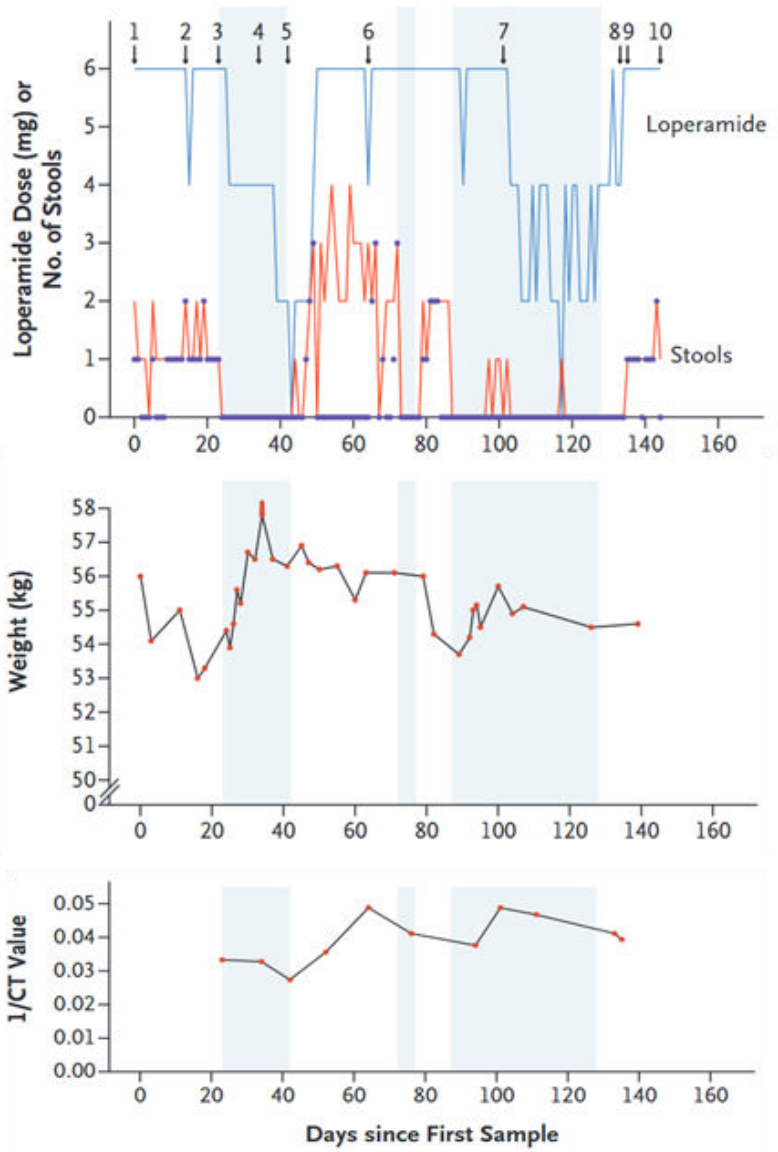
- direct inhibition of viral RdRp
- used in treatment for flu (Japan), phlebovirus (SFTS)
- liver toxicity

Treatment outcomes

- **weight gain + reduced diarrhea**
- but **no resolution of the chronic norovirus infection**



Kreins *et al.*, 2024



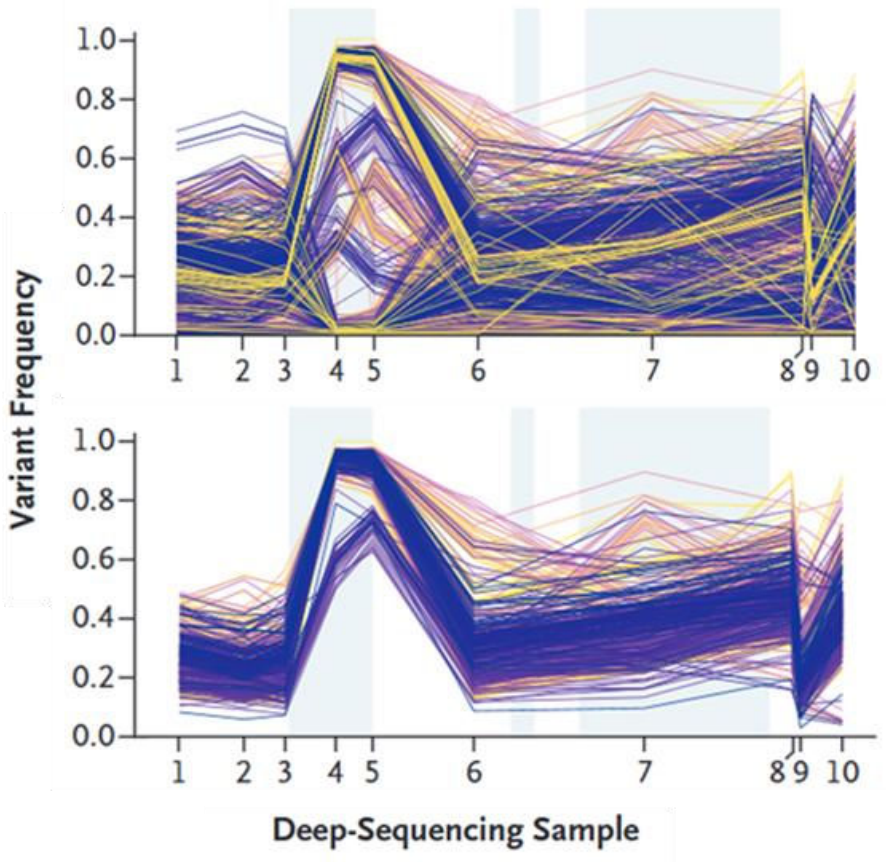
Ruis *et al.*, 2018

Favipiravir: viral mutagenesis and infectivity loss

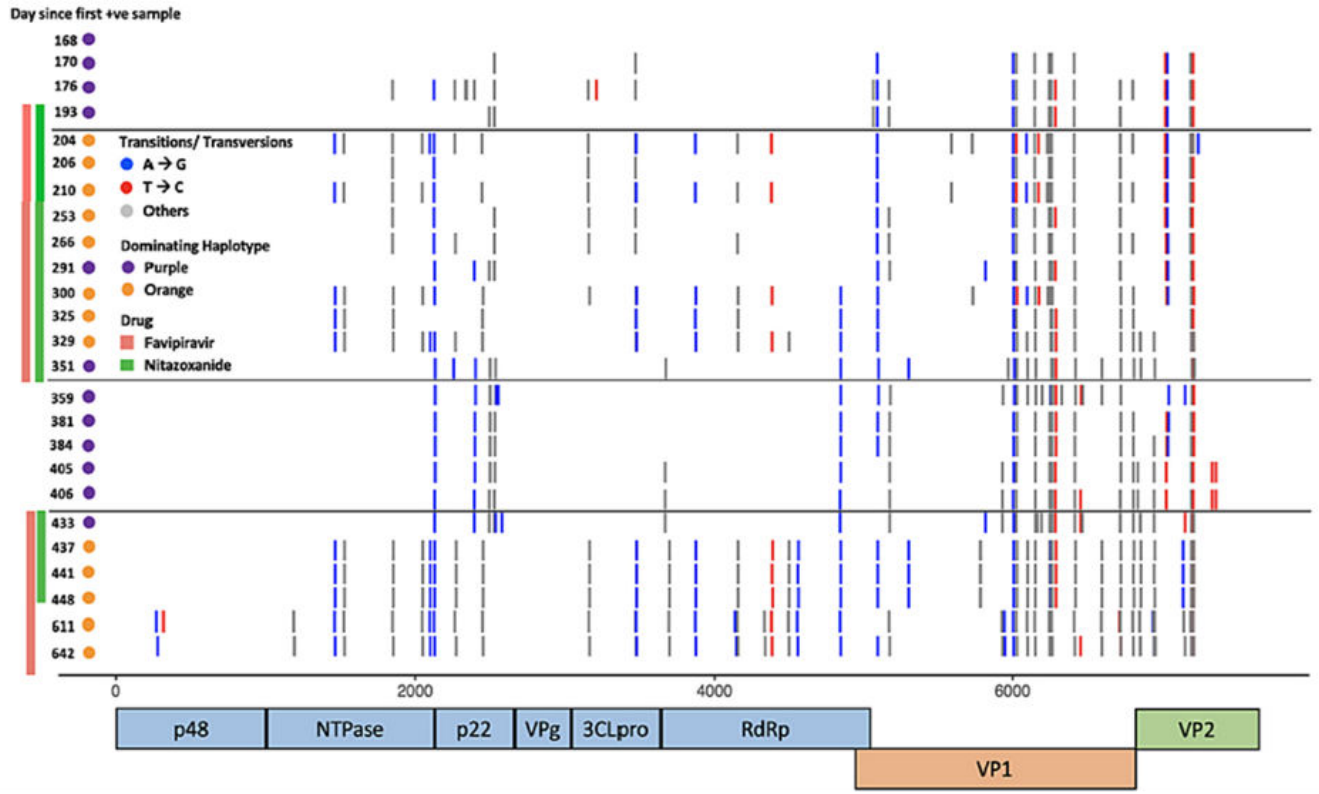
AVIGAN **(favipiravir)**

Induction of multiple point mutations ➔ quasispecies

- accumulation of mutations induces **loss of viral infectivity and fitness** (in Zf experiments)
- **occurrence of RdRp variants** potentially causing favipiravir resistance (in Zf experiments)



Ruis *et al.*, 2018



Kreins *et al.*, 2024

Molnupiravir: inhibition of replication in 3D-HIE

LAGEVRIO (**molnupiravir**)

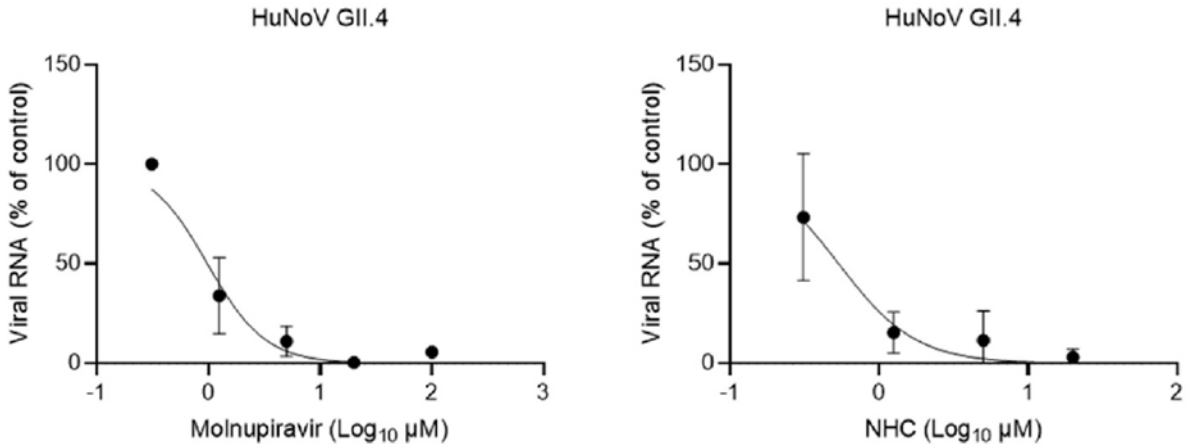
Cytidine nucleoside analogue

- N4-hydroxycytidine (NHC)
- broad-spectrum antiviral against RNA viruses (SARS-CoV-1/2, MERS, Flu, RSV, HCV, VEEV, Ebola)

Active on NoV replication in HIEs

More studies needed

Compassionate treatment for CNI patients?



Molnupiravir inhibits human norovirus and rotavirus replication in 3D human intestinal enteroids

Nanci Santos-Ferreira [a], Jana Van Dycke [a], Winston Chiu [a], Johan Neyts [a], Jelle Matthijnssens [b], Joana Rocha-Pereira [a,*]

Antiviral activity of compounds against NoV GII.4

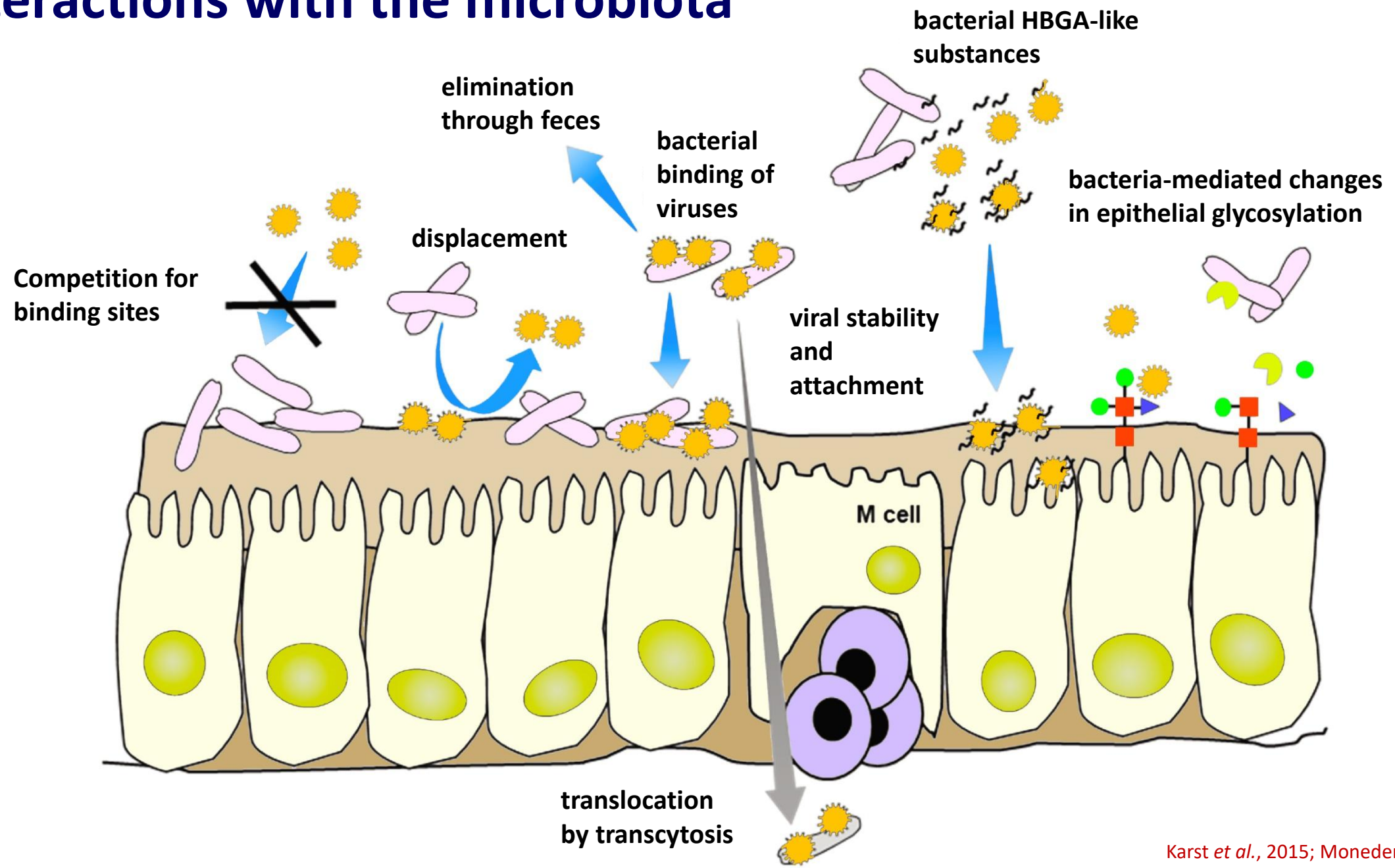
Compound	CC_{50} [a] (µM) – 95% CI [b]	HuNoV GII.4-GII.P4	
		EC_{50} [c] (µM) – 95% CI	SI [d]
Nitazoxanide	139.9 (105.2–202.8)	0.6 ($3.4x10^{-6}$ – 1.7)	233
2CMC	>200	0.2 (0.1–0.3)	>1000
7DMA	>200	4.0 (1.3–8.7)	>50
Favipiravir	>1000	82.1 (53.3–120.7)	>12
Dasabuvir	45.5 (37.8–50)	3.8 (0.2–8.4)	12

Virus	HuNoV GII.4		
	CC_{50} [a] (µM)– 95% CI [b]	EC_{50} [c] (µM)– 95% CI	SI [d]
Molnupiravir	>200	1.0 (0.6–1.4)	>200
NHC	>200	0.5 (0.3–0.8)	>400

[a] CC_{50} half-maximal cytotoxic concentration.
[b] CI confidence interval.
[c] EC_{50} half-maximal effective concentration.
[d] SI selectivity index

Santos-Ferreira *et al.*, 2024

Interactions with the microbiota



Karst *et al.*, 2015; Monedero *et al.*, 2018

Fecal microbiota transplantation: an alternative?

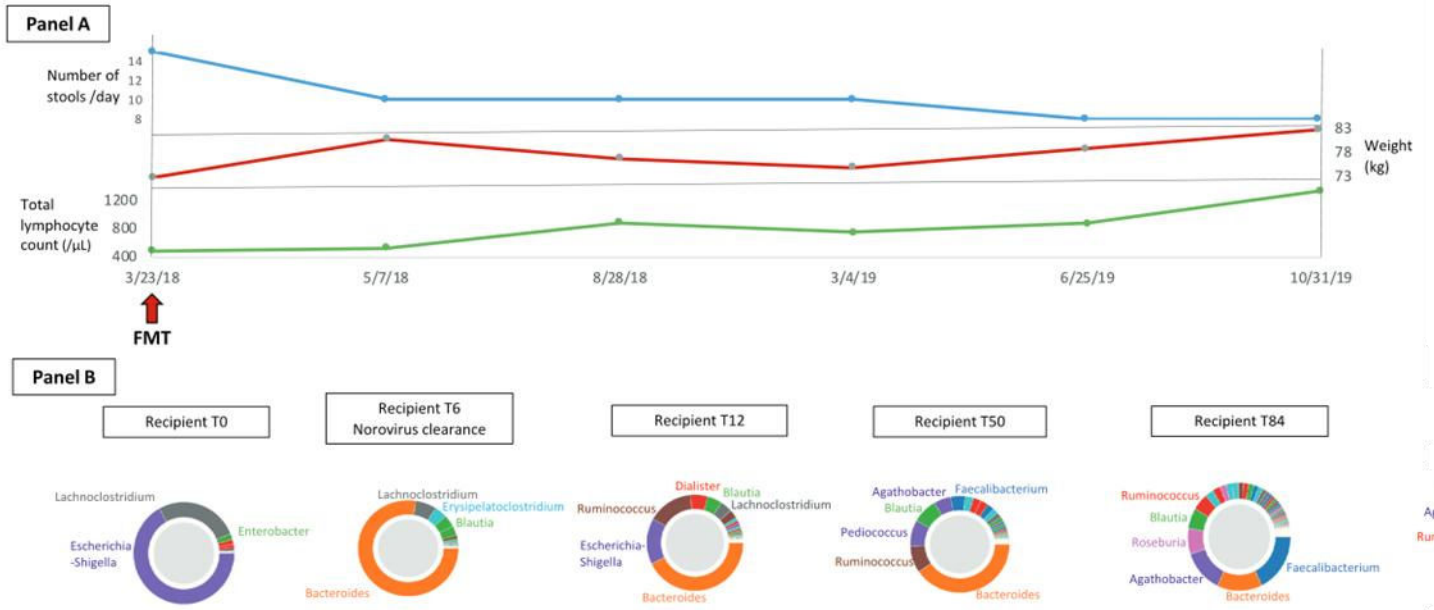
Gut microbiota interacts with norovirus

- antiviral or proviral effects of certain bacteria species
- enhancement of virus attachment facilitates infection

FMT benefits in refractory chronic NoV infection

- restoration of bacterial flora and **clinical improvement** of diarrhea
- nonbacterial content supply: bacterial short-chain fatty acids, host immune effectors, other metabolites

➔ **immunoglobulins** in feces: potential effector of FMT therapeutic effects

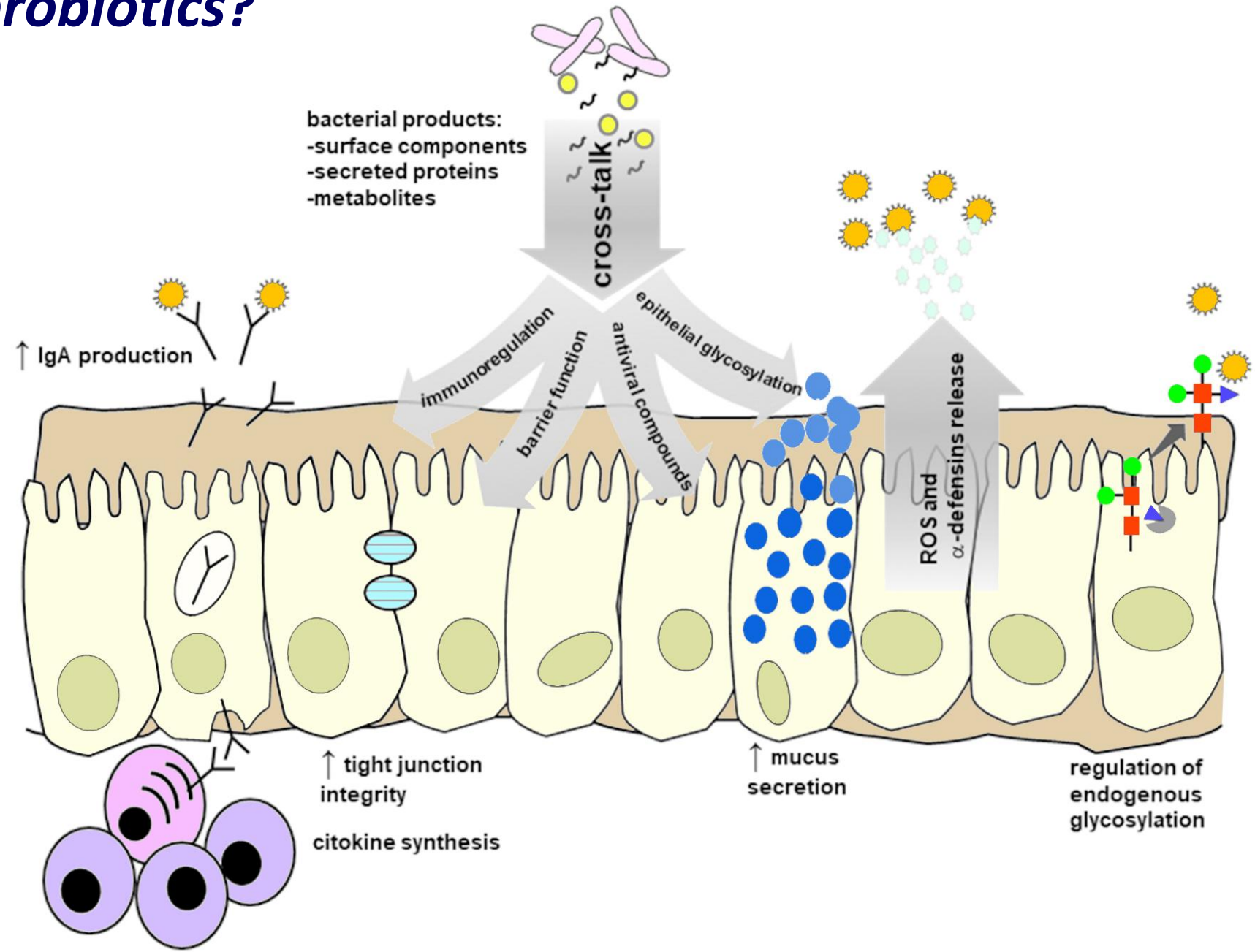


Clinical remission after faecal microbiota transplantation in transplanted recipients with refractory chronic Norovirus infections: a retrospective case series

Sarah Soueges [1,*], Valérie Cheynet [2], Thomas Briot [3,4], Claire Merveilleux du Vignaux [5], Nicolas Benech [4,6,7,8], Florence Ader [1,4,8,9]

Souesges *et al*,, 2024

Role of probiotics?



Monedero *et al.*, 2018

Infection control and vaccination

Universal precautions + cross-transmission barriers

– **hand hygiene ++ =** washing before and after care
+ hydroalcoholic solution (70%) ➔ *virucidal standard NFEN 14476* *(adeno/polio)* ***+++***

– protective gloves, mask, goggles, clothing

– disinfection/sterilization of medical devices

– appropriate environmental decontamination +

– patient isolation ++

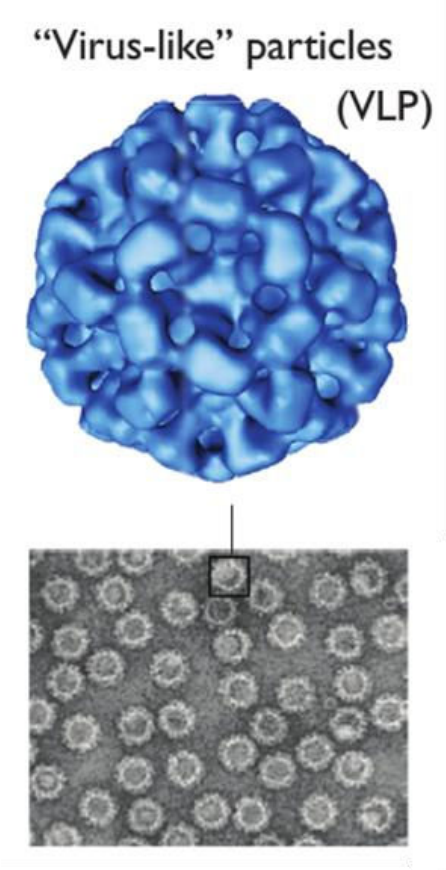
Vaccine development

– based on **virus-like particles (VLPs) of GI + GII NoVs**
➔ self-assembly of VP1 capsid proteins / lack of viral genome

– inoculation routes: intranasal, intramuscular, subcutaneous, oral

– elicit good levels of neutralizing antibodies and cell immunity

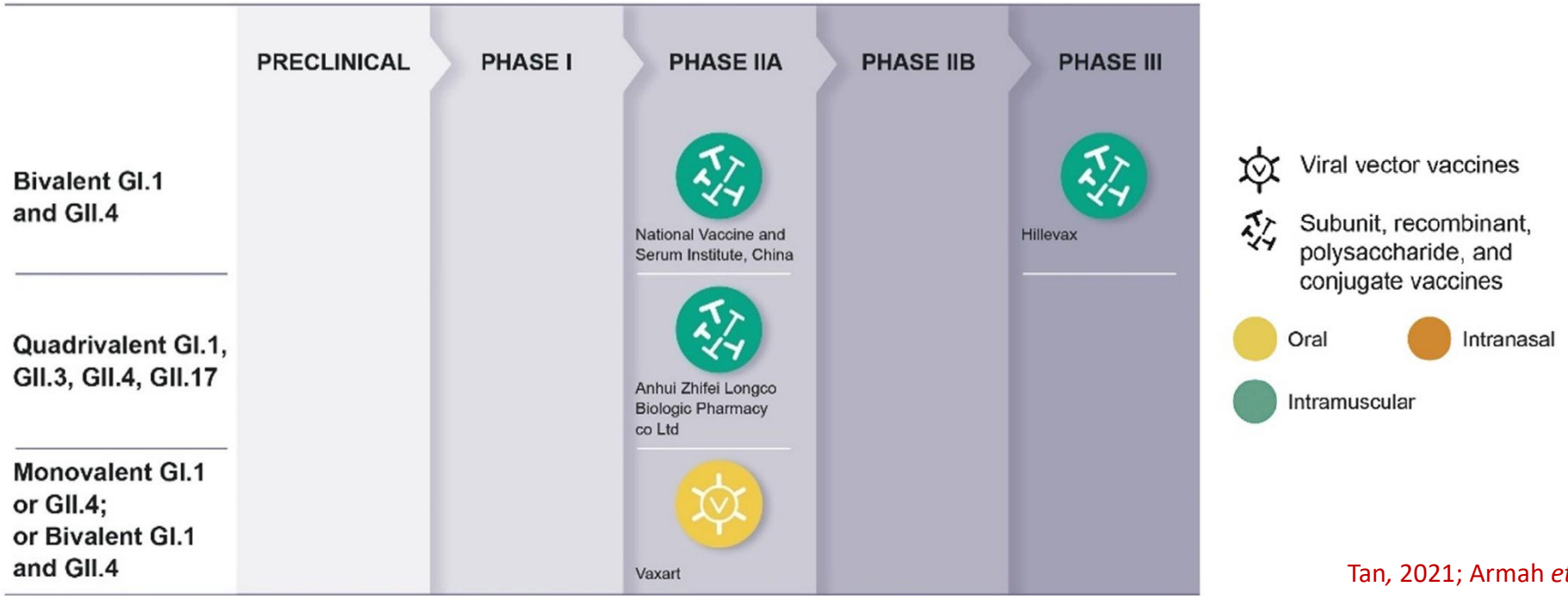
– currently 4 vaccines are under development



Green, 2013

Current developments in norovirus vaccines

Company	Vaccine Candidate	Adjuvant	Administration Route	Antigen Format	Antigen Genotype
Takeda	TAK-214	Chitosan/MPLA, aluminum salt	Intranasal, intramuscular	Noroviral VLP	GI.1/GII.4
Vaxart	VXA-NVV-104	Adenovirus expressing double-stranded RNAs	Oral	Adenovirus expressing noroviral VP1	GI.1/GII.4
NVSI	Hansenulapolymorpha	Aluminum salt	Intramuscular	Noroviral VLP	GI.1/GII.4
IPS/Zhifei	Longkoma	Aluminum salt	Intramuscular	Noroviral VLP	GI.1/GII.3/ GII.4/GII.17

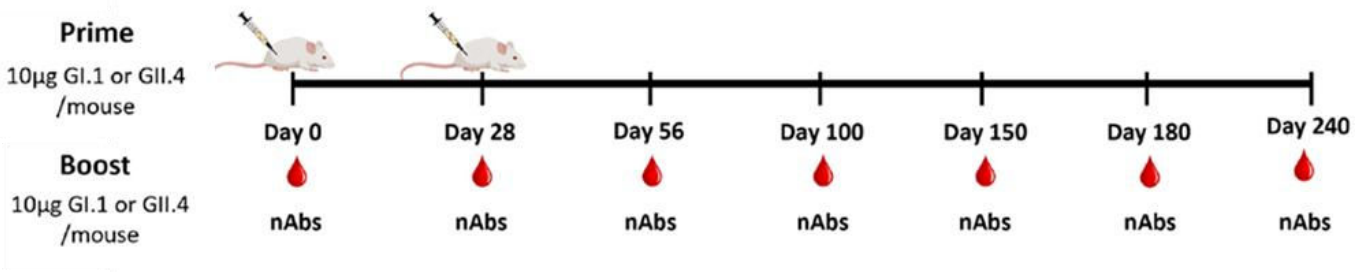


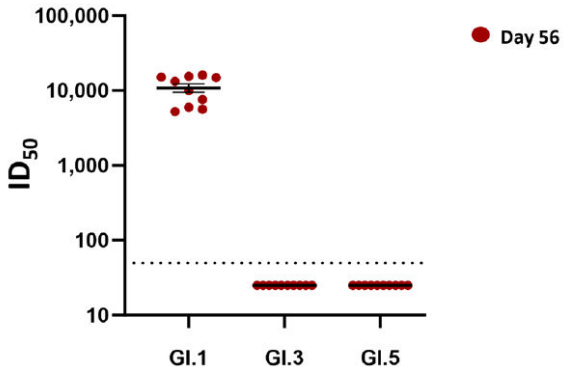
Tan, 2021; Armah *et al.*, 2023

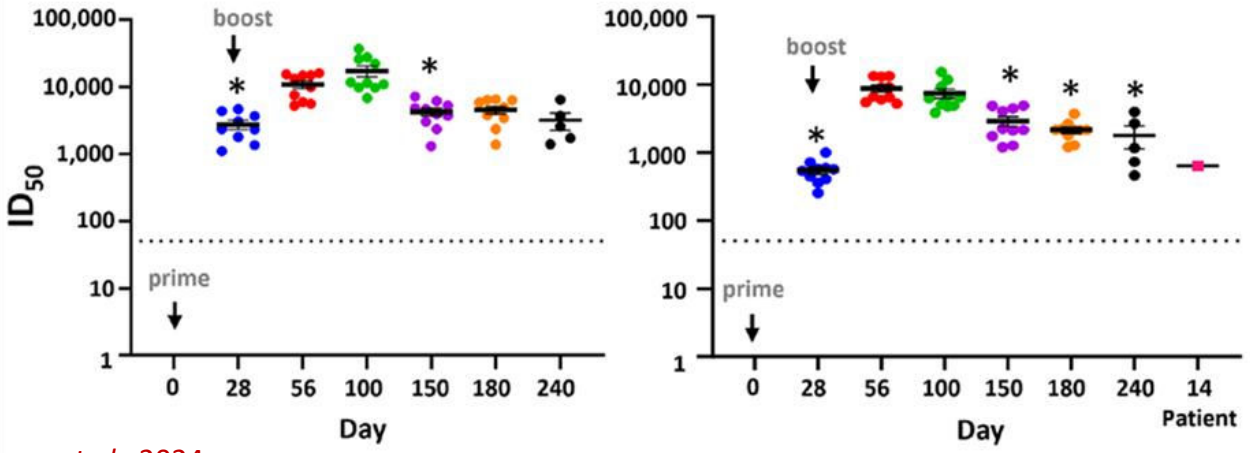
Development of a bivalent mRNA vaccine

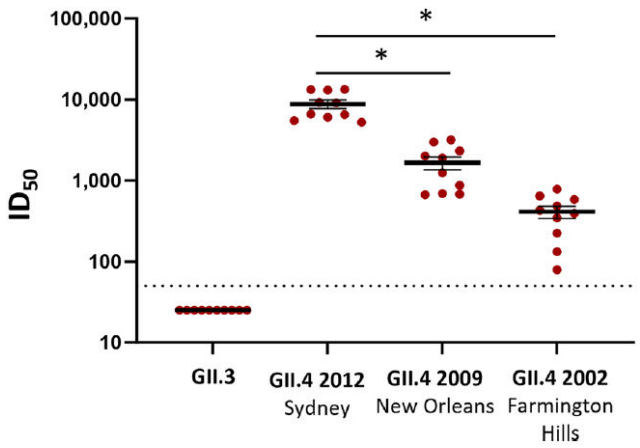
mRNA-Lipid nanoparticle vaccine platform ← VP1 capsid protein of GI.1 and GII.4 NoVs

➔ high levels of neutralizing antibodies through strong genotype-specific responses
robust cellular responses
effective on protecting human enteroids from infection









Atochina-Vasserman *et al.*, 2024

Conclusion on chronic norovirus infections

Norovirus

– main agent of AGE (= **fecal peril**)
– CNI: particularly challenging infection in immunocompromised
– **therapeutics still under development**
  - no real specific and effective drugs
  - compassionate treatment?
– being aware of the rise of sapovirus or Aichi virus chronic infection cases

Future perspective and challenges

– **Urgent need to discover new effective drugs on chronic infections**
– **Extension of the use of HIE for drug testing**
  - better contribution to the development and evaluation of new drugs or compounds
  - **development of a personalized medicine approach** using patient's intestinal biopsy
  - but the use of organoid culture is limited: replication limitation, fastidious and expensive culture
    ➔ future developments needed: organ-on-chip systems, culture media, other enhancement…
– **Better define the role of FMT** in the therapeutic strategy

➔ **Needs for extensive collaborative clinical studies**

BACK TO THE FUTURE

3è Journée Scientifique du Réseau Virus et Greffes

Cité Universitaire Internationale, Paris – January 13, 2025

gastroenteritis viruses
Dijon, France

Université Bourgogne Europe