

Innate Immunity

M&I 104/204

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<http://cmgm.stanford.edu/micro/Schneider-lab/home.html>

Two arms to the human immune system



Innate: born with it



Adaptive

-Specific

-Acquired

-RAG dependent



Names are important

Pro-choice vs Pro-life

French fries vs freedom fries

Canola vs rapeseed

Broccoli rape vs broccolini

Healthy skies initiative

Two arms to the human immune system



Innate: born with it



Adaptive

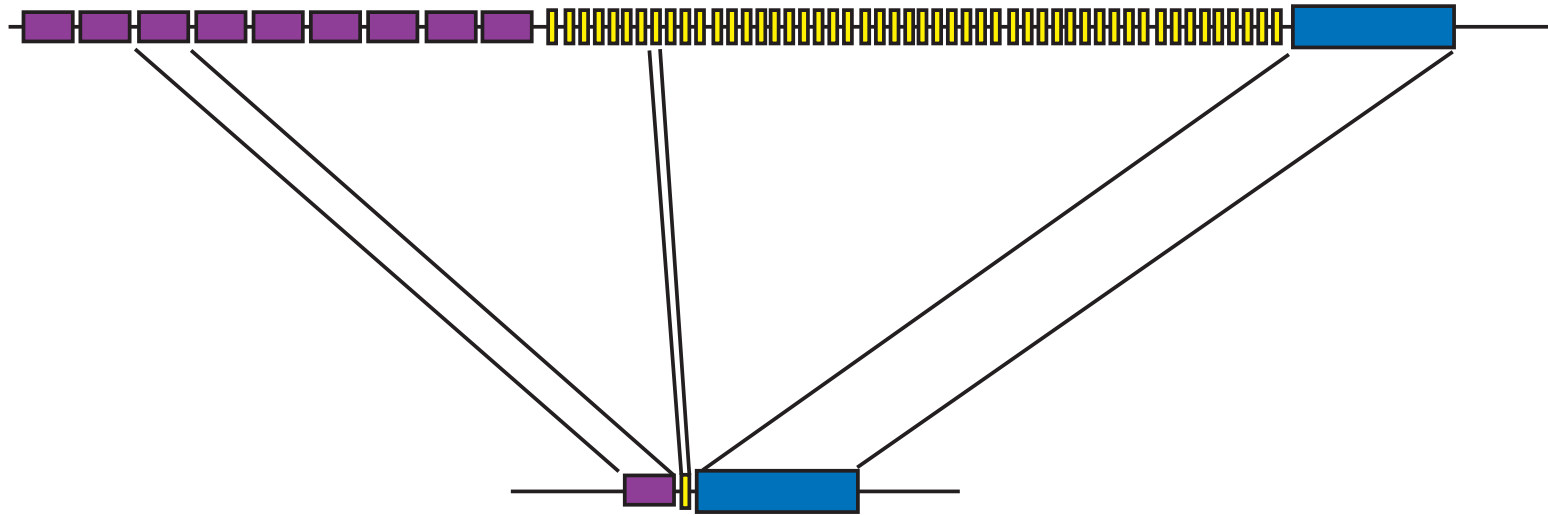
-Specific

-Acquired

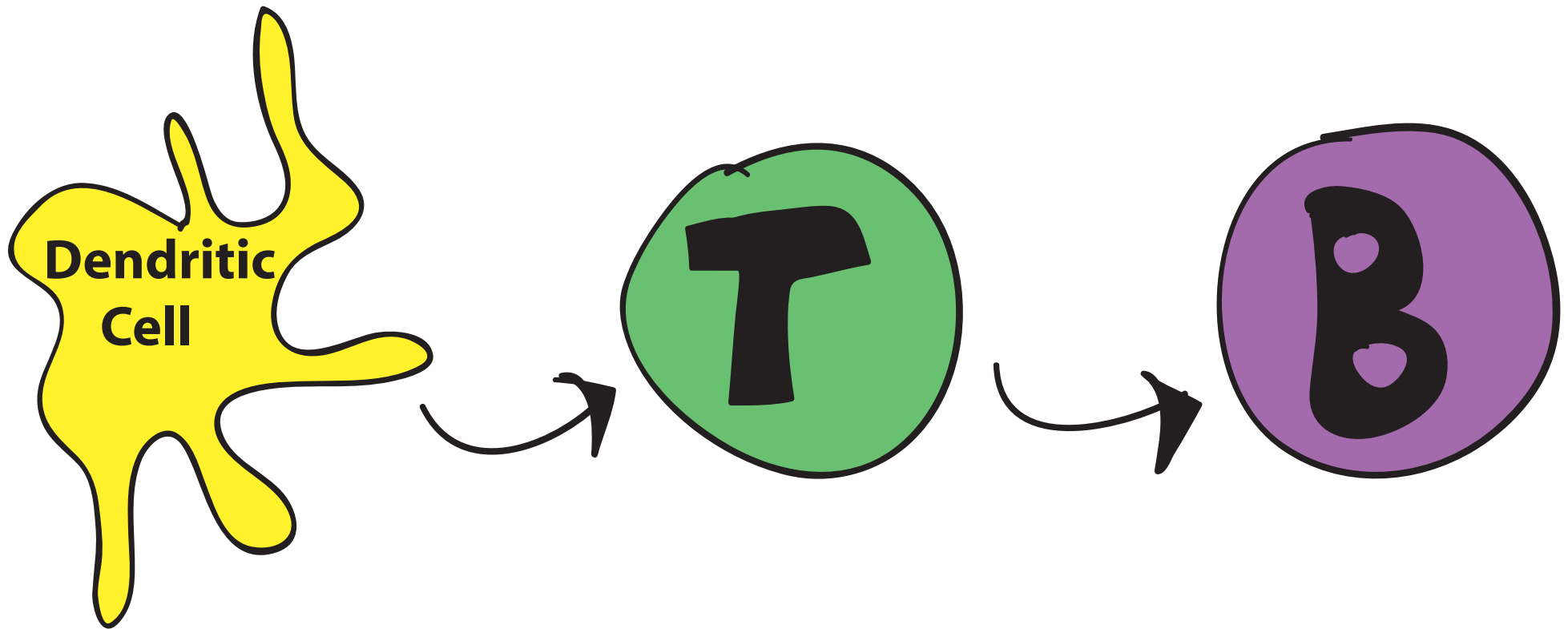
-RAG dependent



Adaptive immune responses depend upon somatic recombination to produce variation



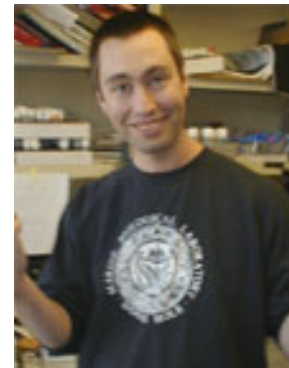
Logic of the RAG immune response



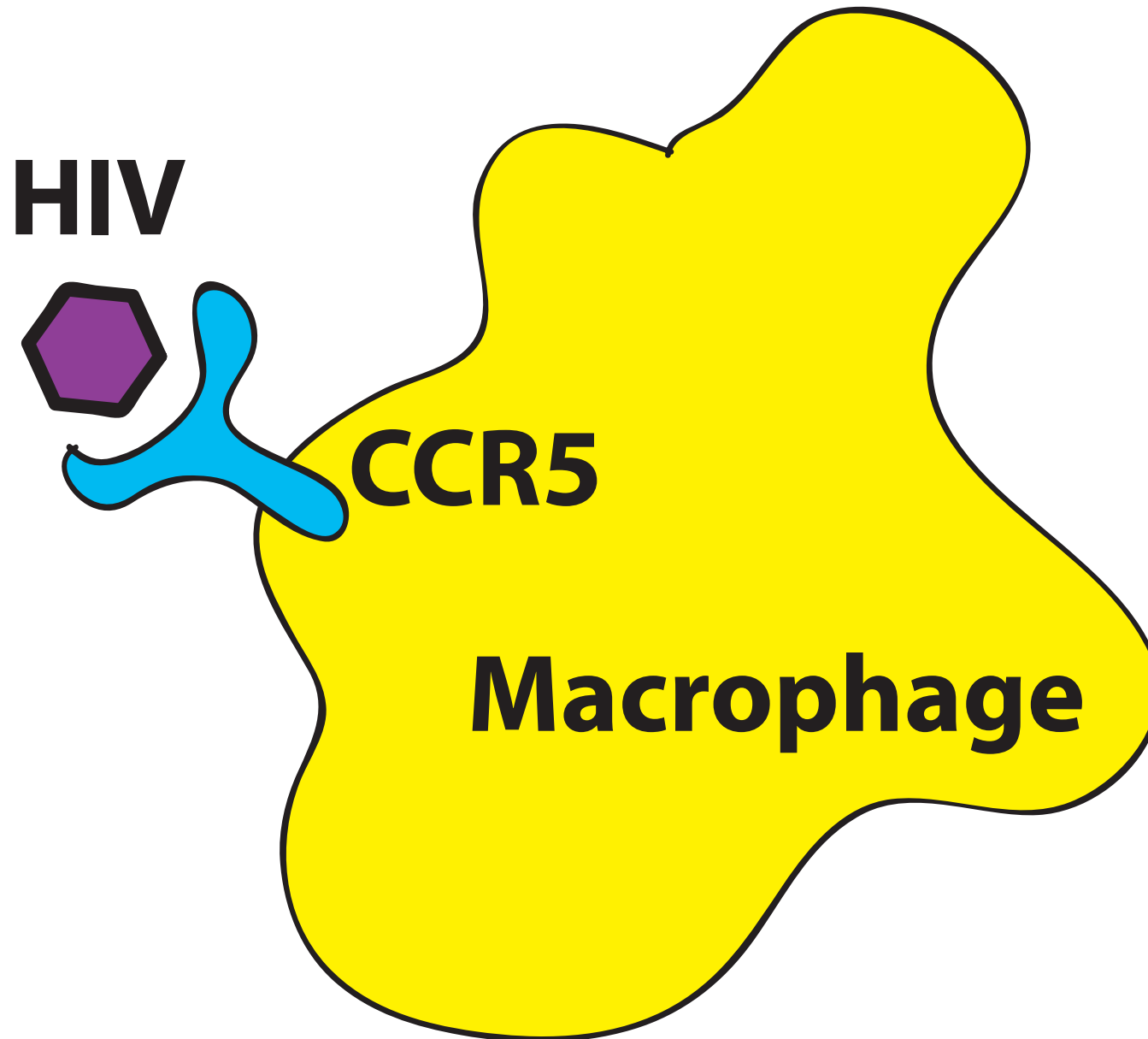
Why study innate immunity?



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Simple mutations can provide immunity



Our surfaces are protected by antimicrobial compounds and have a native flora



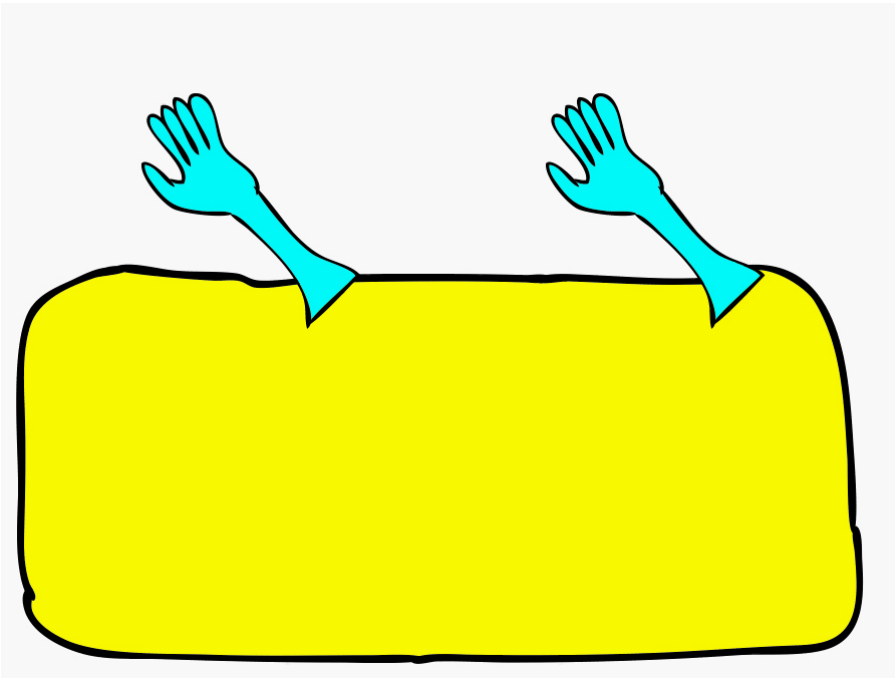
**bacteria from
hand**



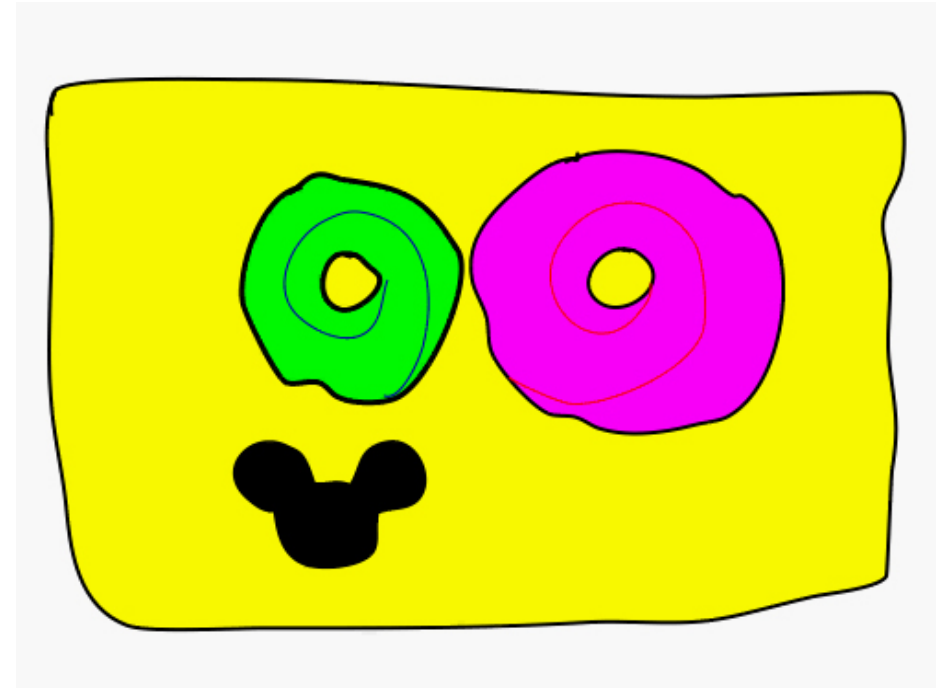
sneeze bugs

<http://www.ces.uga.edu/pubcd/B693.htm>

Activation of innate immune signaling



Pattern Recognition



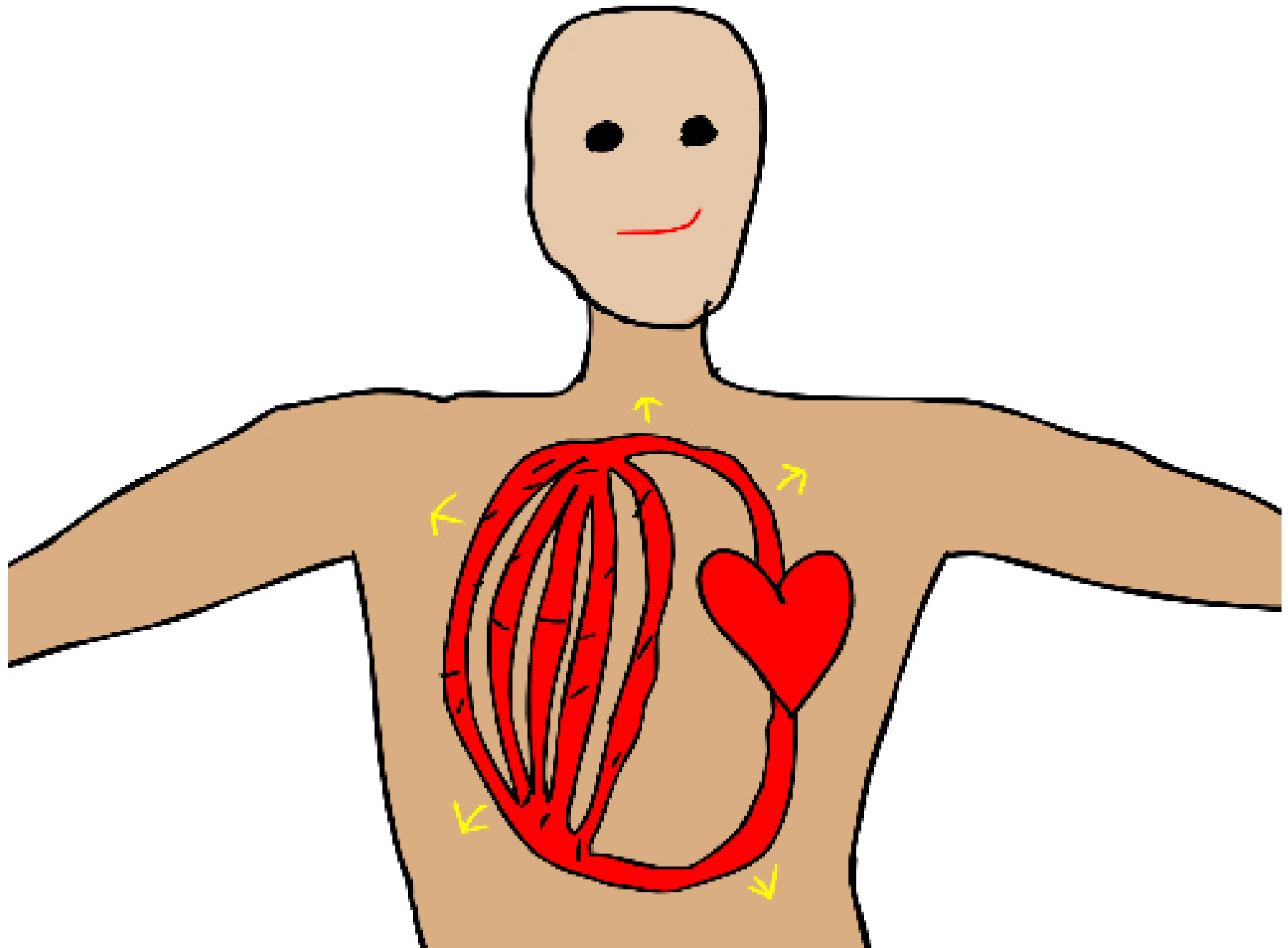
**Alteration of host
metabolism**

Cells and soluble factors fight infections inside the body

3b

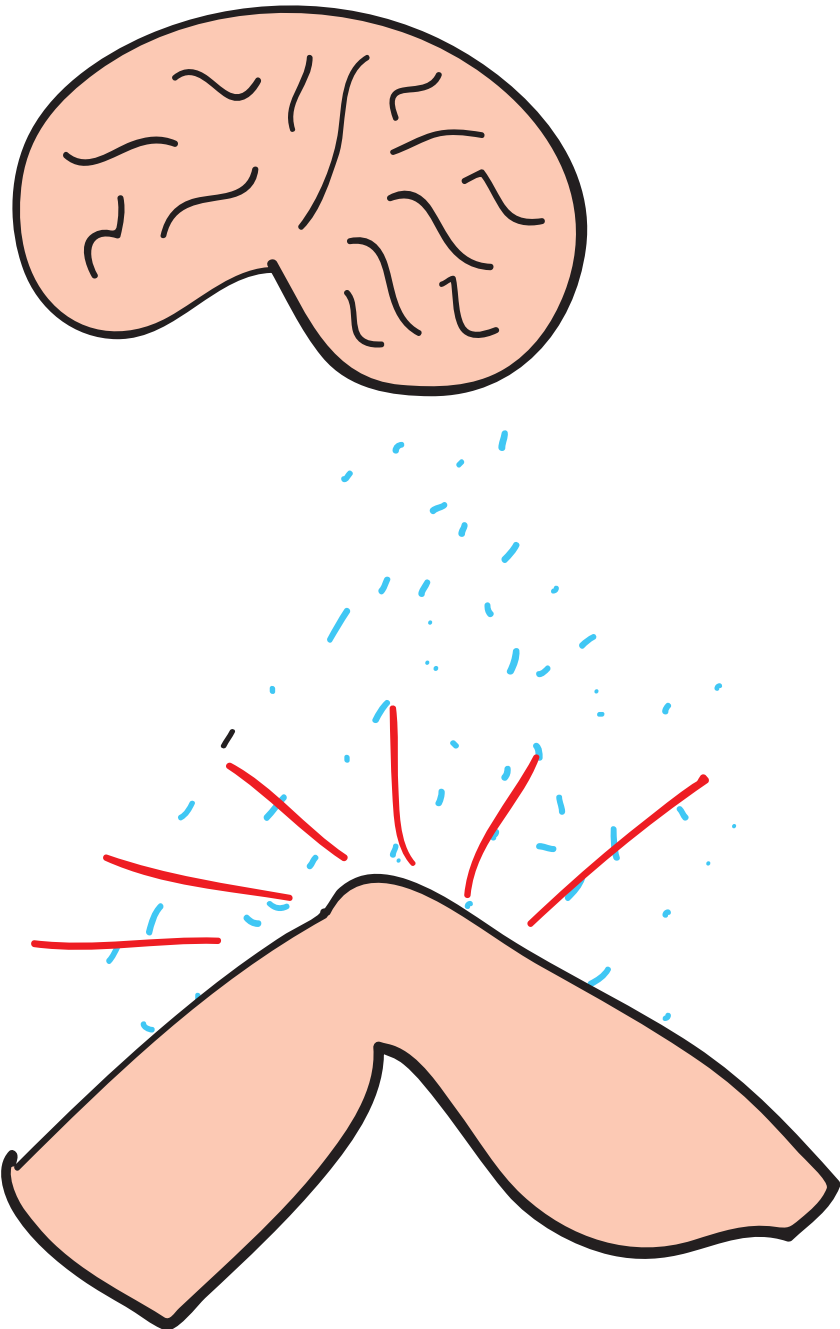


Innate physiological responses to infection can produce pathology

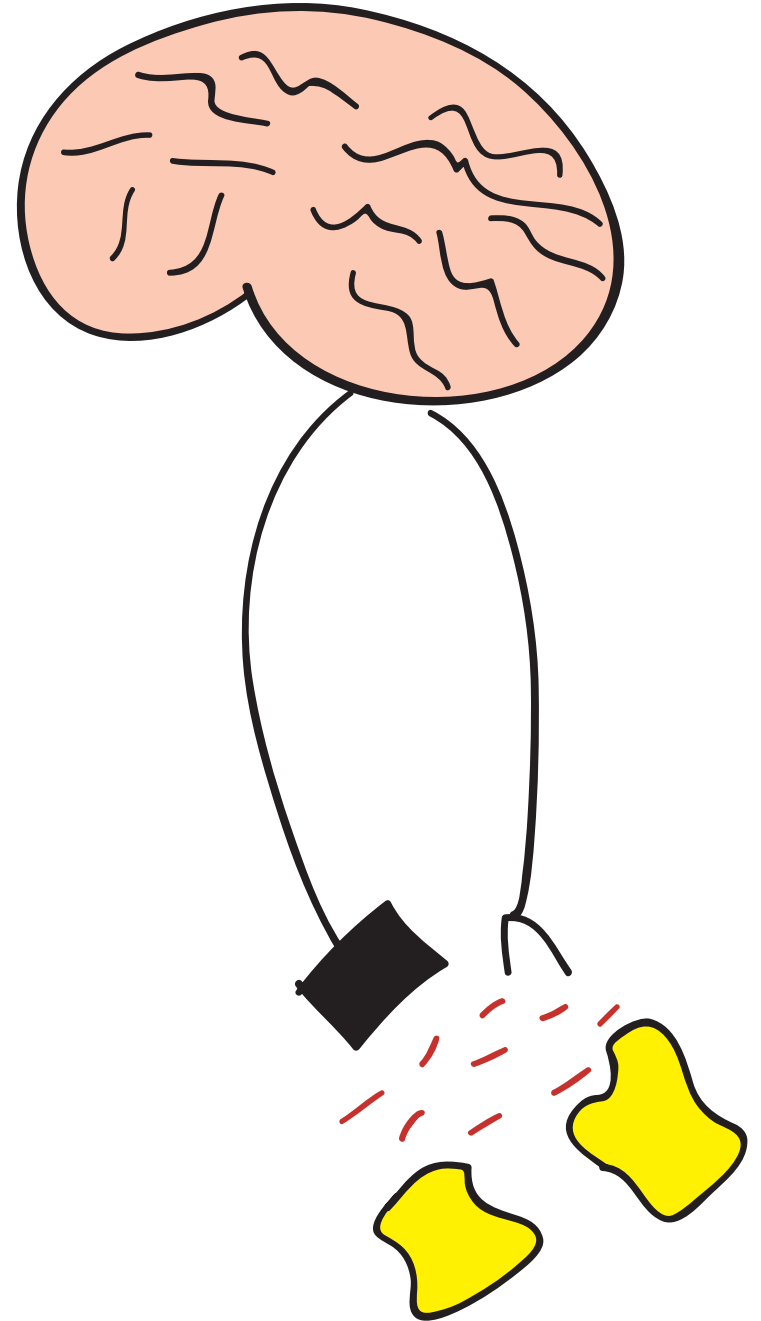


The brain is an innate immune organ

glucocorticoid release



direct neural signaling



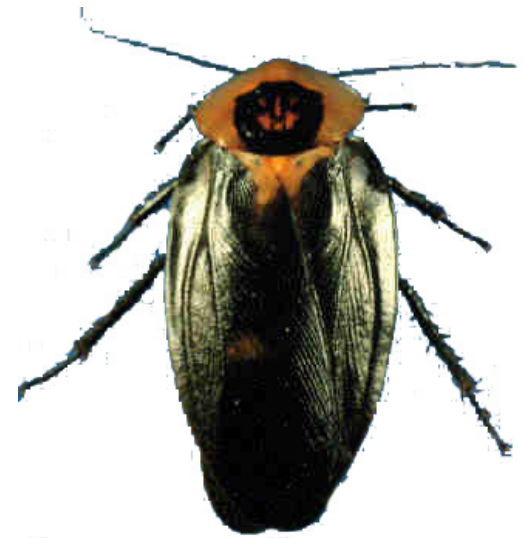
Are there behavioral contributions to innate immunity?



Memory and the innate immune response



Vaccinate



Challenge

Not all hosts are created equal

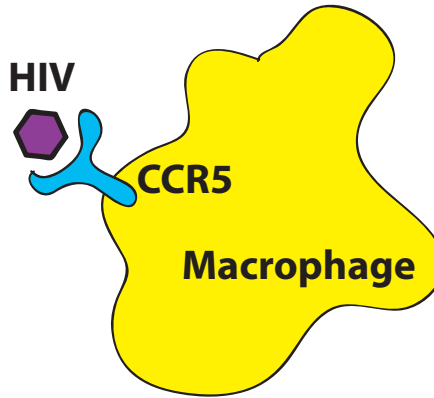


Polymorphisms and infectious disease

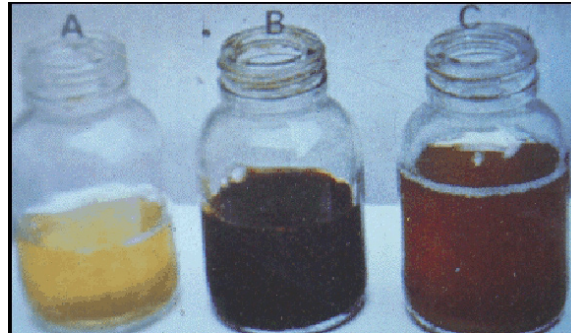
Disease	Gene	Mechanism
Malaria		
	G6PDH	alters redox balance
	Hemoglobin : sickle cell anemia	?
	TNF Promotor	over-reaction to infection
	Thalassemia	?
	Hemoglobin	?
	CCR2	P. vivax receptor
Typhoid fever		
	CFTR: cystic fibrosis gene	S. typhi receptor
AIDS		
	CCR5	HIV receptor
	Enhanced NK activity	?
Leprosy		
	TLR 2	poor cellular response
Ngana		
	TLF	lytic factor kills parasite
Sepsis		
	Factor V ^{Leiden}	?

Basic themes

Missing receptors



Altered pathogenesis



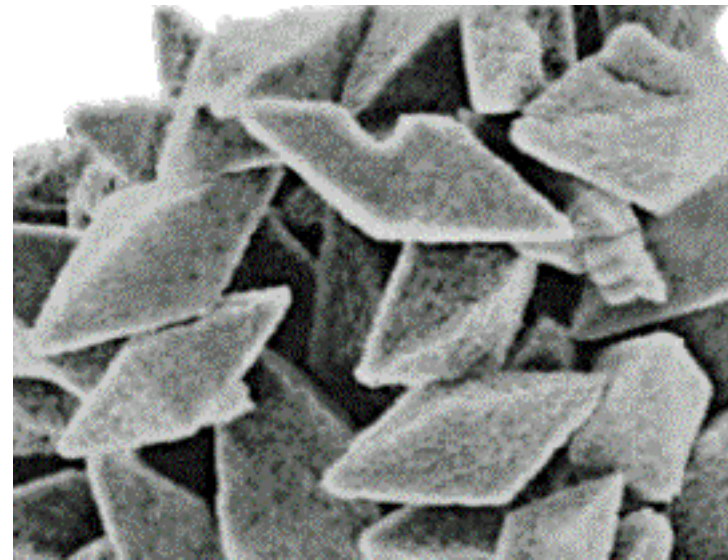
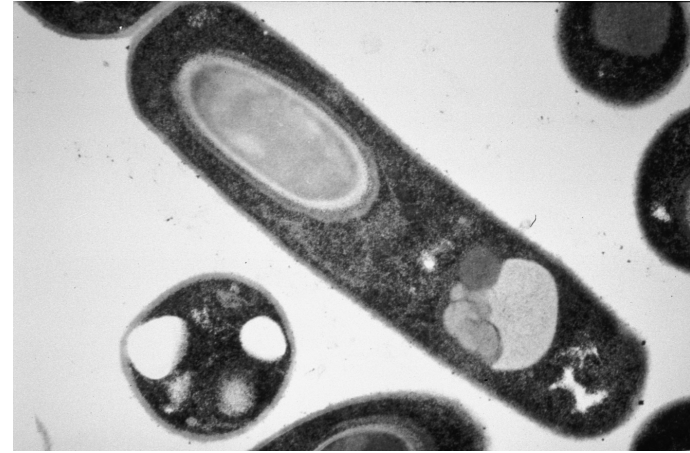
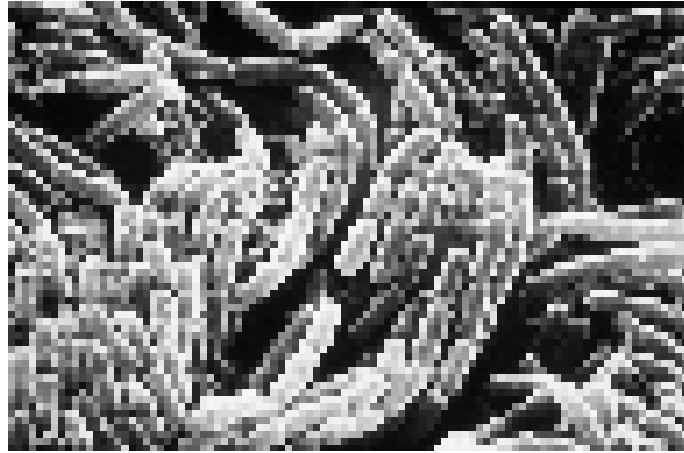
Wrong environment



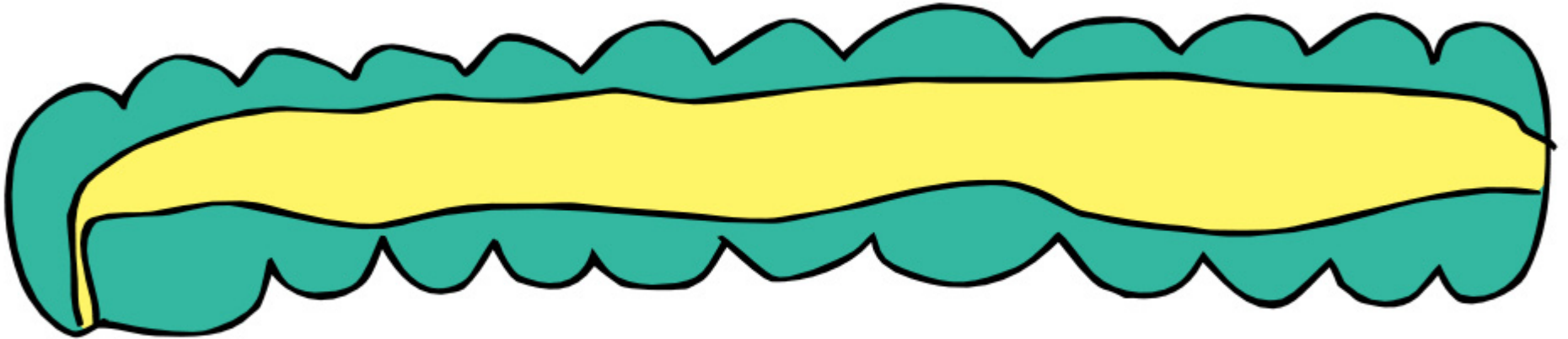
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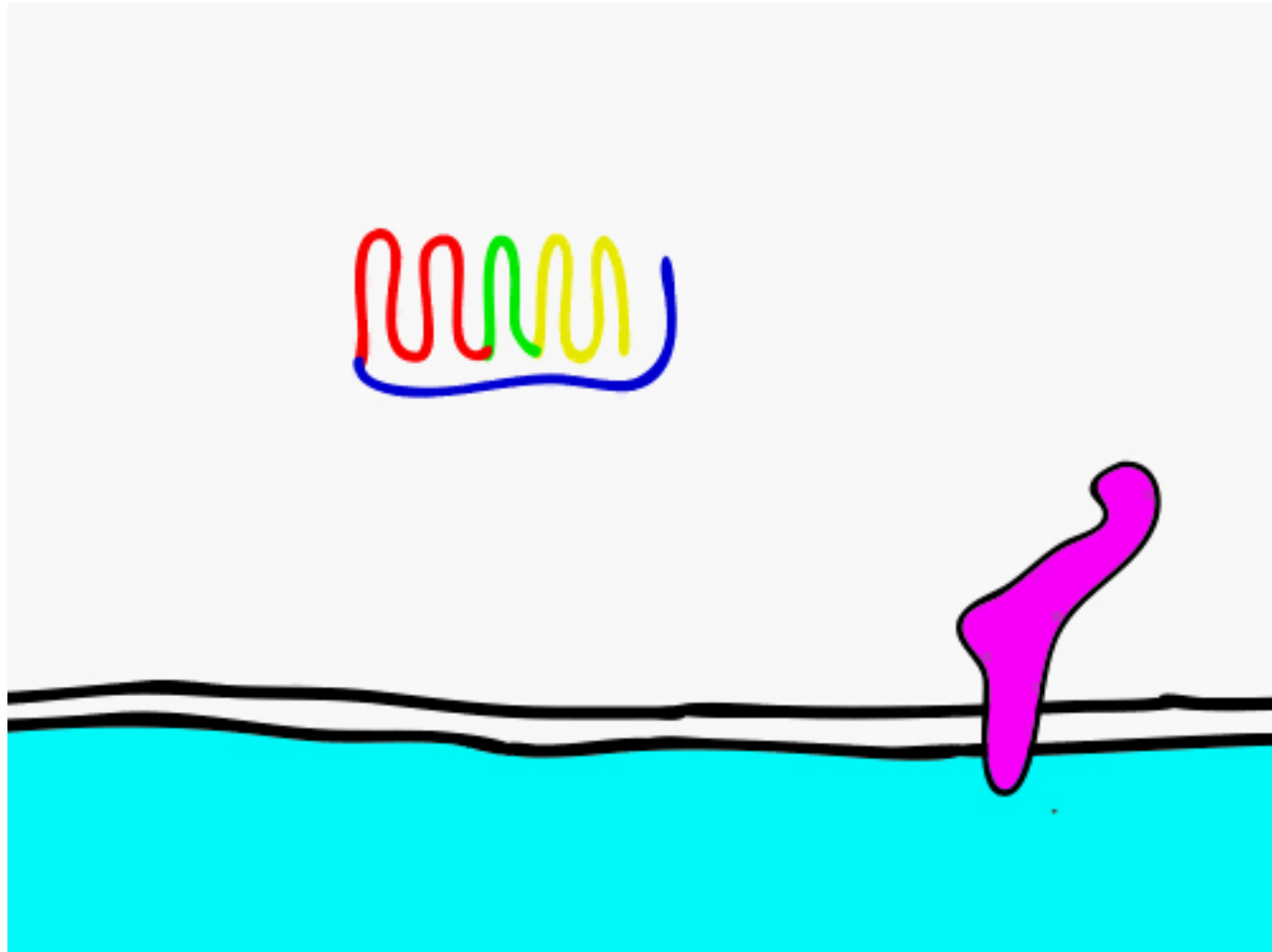
Bacillus thuringiensis causes lethal infections in a variety of insects



B.thuringiensis is infectious orally



**The delta-endotoxin must first be
cleaved before it binds
its receptor**



Transgenic crops are useful for fighting insects that are hard to reach by spraying



Not everyone agrees this is a good idea



The **HORROR** of Genetically Engineered Food

IT from the **Came Grocery Store**

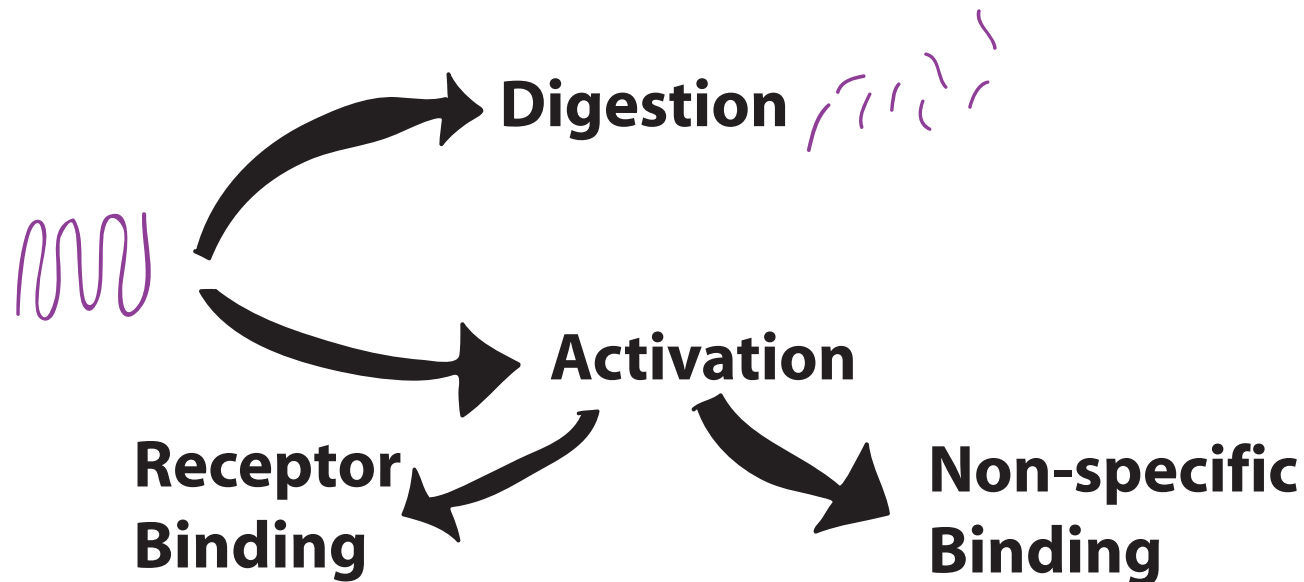
You Can't Avoid It Because It's **NOT LABELED!**

GREENPEACE

From the **LABS** of Monsanto to **YOUR TABLE!**
A **NEW LIFE FORM** Released into the World!

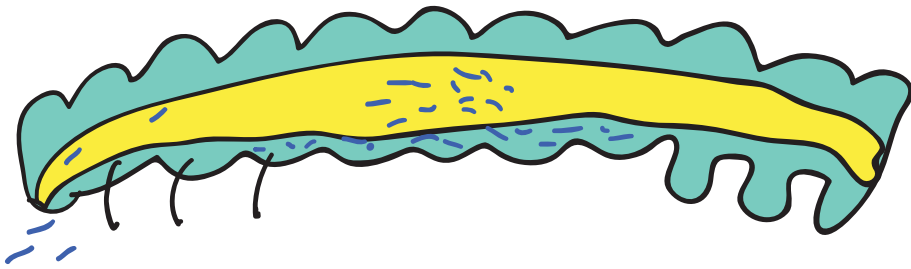
© 2001 Greenpeace

Insects can mutate in a variety of manners to become resistant

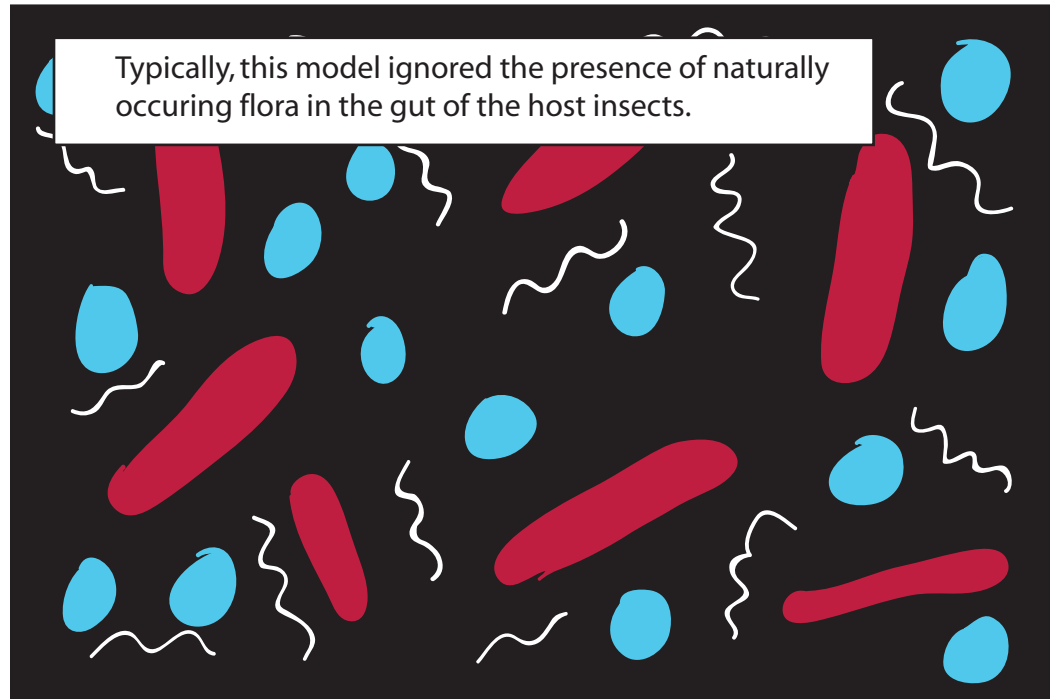


Species	mechanism
P. interpunctella	= activation, low binding
P. interpunctella	reduced activation, = binding
S. exigua	increased non-specific binding
H. virescens	reduced activation, increased degradation

Early models assumed that B.t. and B.t. toxin were the only components required to kill their hosts. The toxin was predicted to punch a whole through the gut and this lead to starvation or the invasion of B.t.



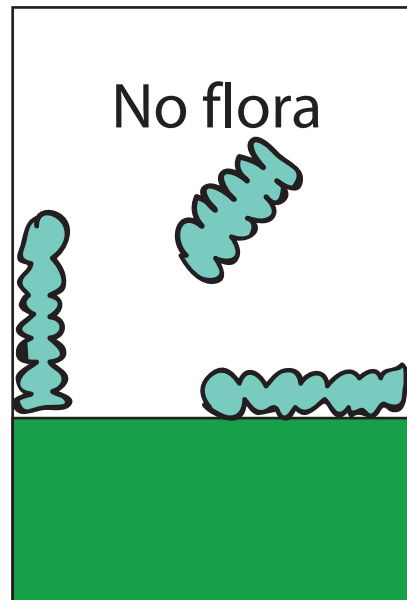
Typically, this model ignored the presence of naturally occurring flora in the gut of the host insects.



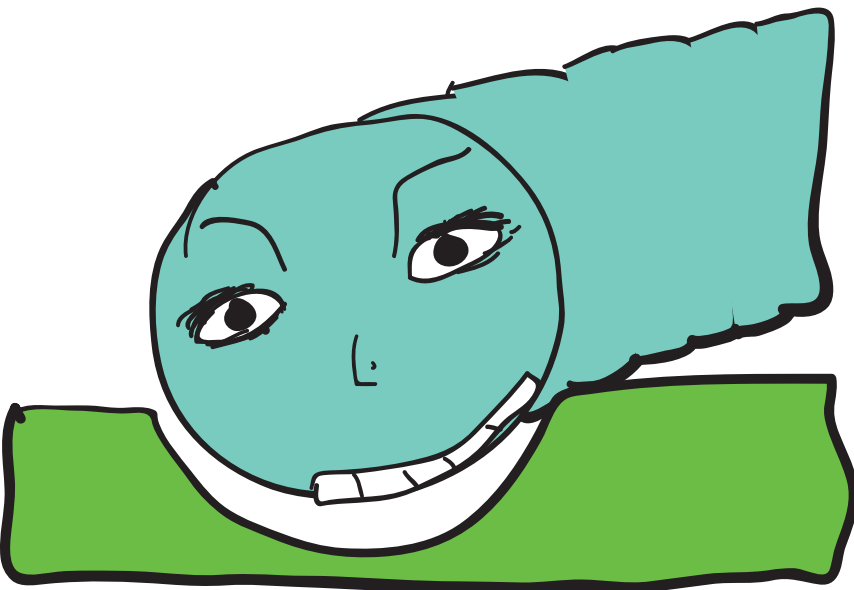
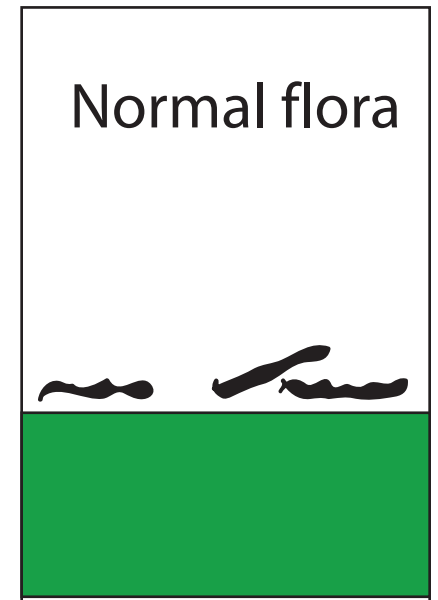
So, Nichole Broderick asked a simple question:
Are native flora important in a B.t. infection?
PNAS. 103. #41, pp 15196-15199, 2006

It turned out that it is the bug's native flora that is the lethal agent when B.t. toxin is present. In the absence of gut flora, B.t. is harmless.

No flora



Normal flora



Plasmodium vivax and the Duffy antigen

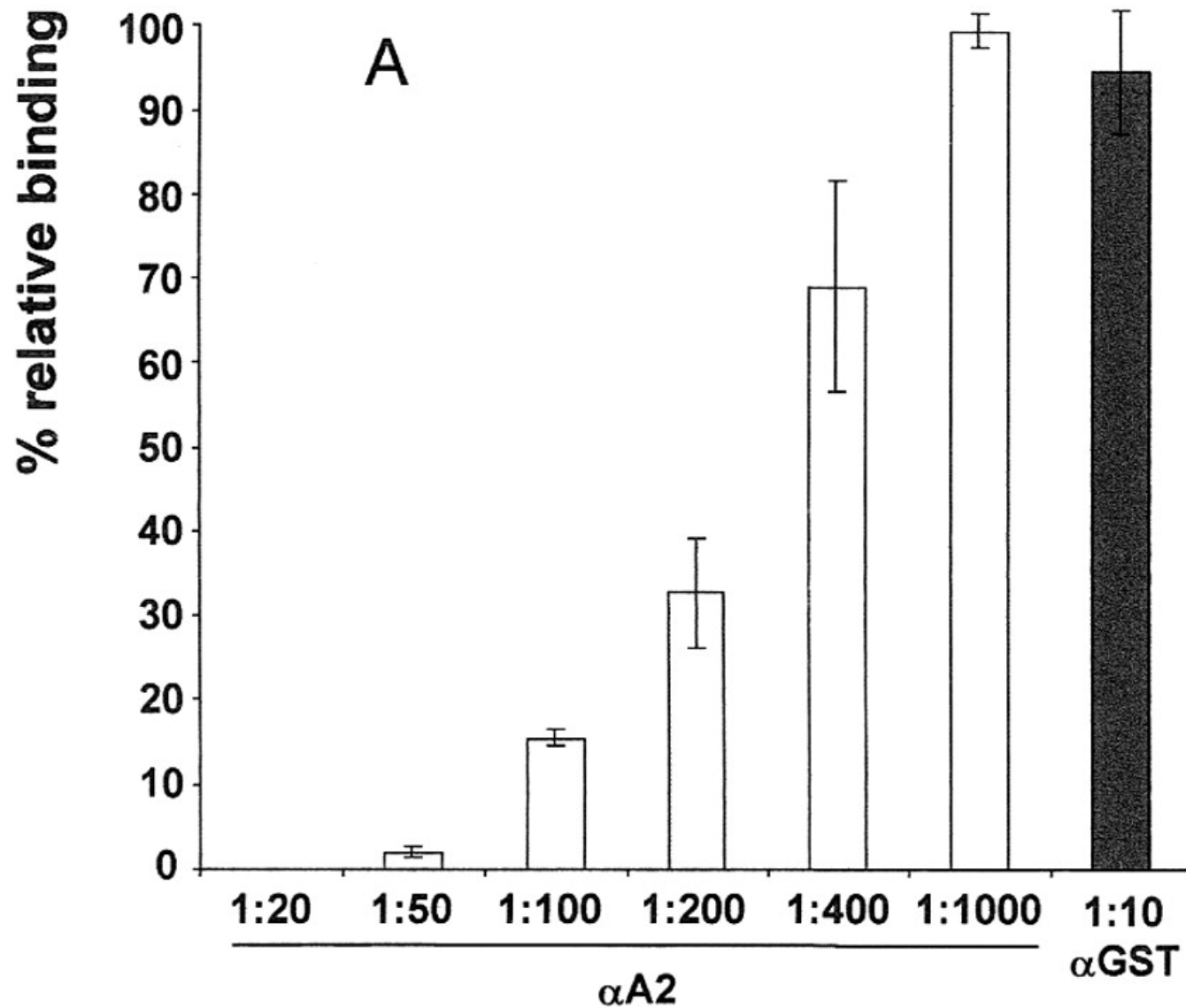
malaria: *P. vivax* entry is mediated by duffy antigen

Table 2. Relation between Resistance to *P. vivax* Malaria, Race and Duffy Blood-Group Phenotype.*

STUDY No.	VOLUNTEER No.	PREPATENT PERIOD†	RACE	PHENOTYPE
I	1	11 days	Black	Fy(a-b+)
II	2	Never patent	Black	Fy(a-b-)
	3	12 days	White	ND‡
III	4	Never patent	Black	Fy(a-b-)
	5	9 days	White	ND‡
IV	6	15 days	Black	Fy(a+b-)
V	7	Never patent	Black	Fy(a-b-)
	8	12 days	Black	Fy(a-b+)
VI	9	Never patent	Black	Fy(a-b-)
	10	Never patent	Black	Fy(a-b-)
	11	14 days	Black	Fy(a-b+)
	12	15 days	Black	Fy(a-b+)
	13	11 days	Black	Fy(a+b-)
	14	12 days	White	Fy(a-b+)
	15	11 days	White	Fy(a-b+)
	16	10 days	White	Fy(a+b+)
	17	12 days	White	Fy(a+b+)

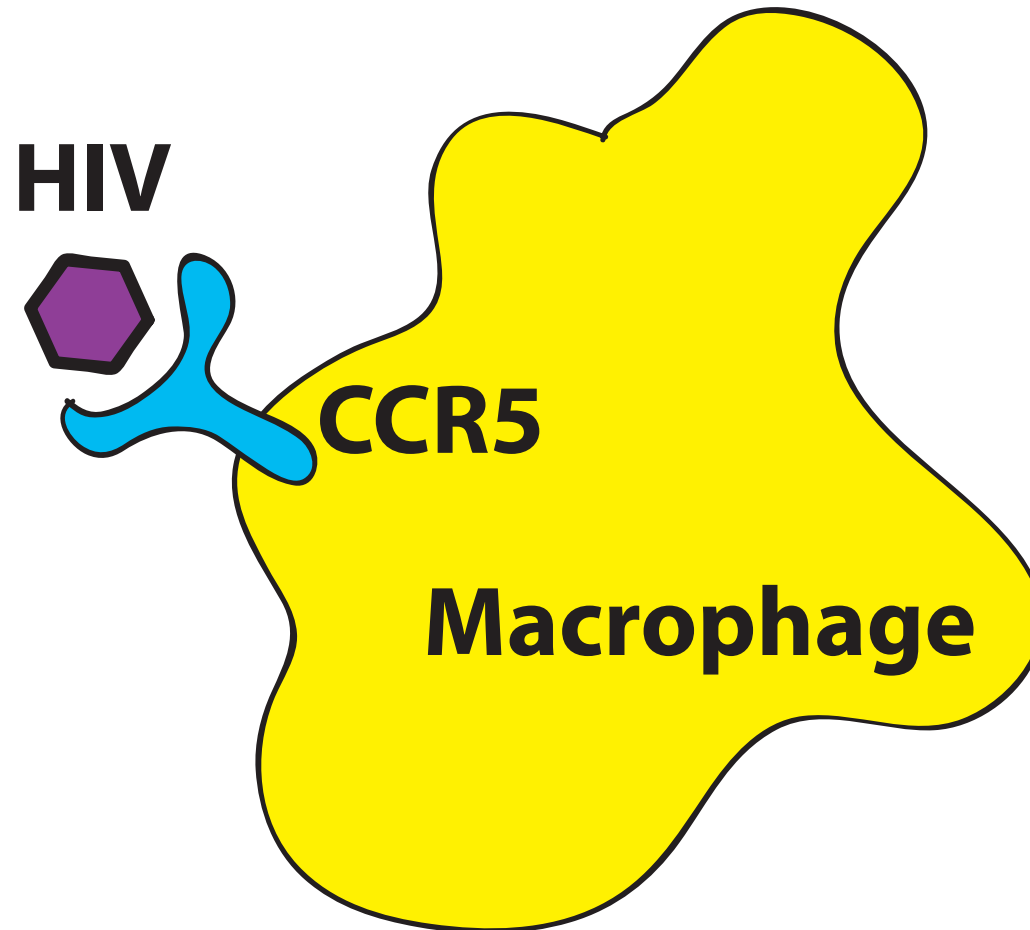
Miller et al. 1976 N Engl J Med 295:302-4

The *P.vivax* duffy binding protein thus makes an interesting vaccine candidate



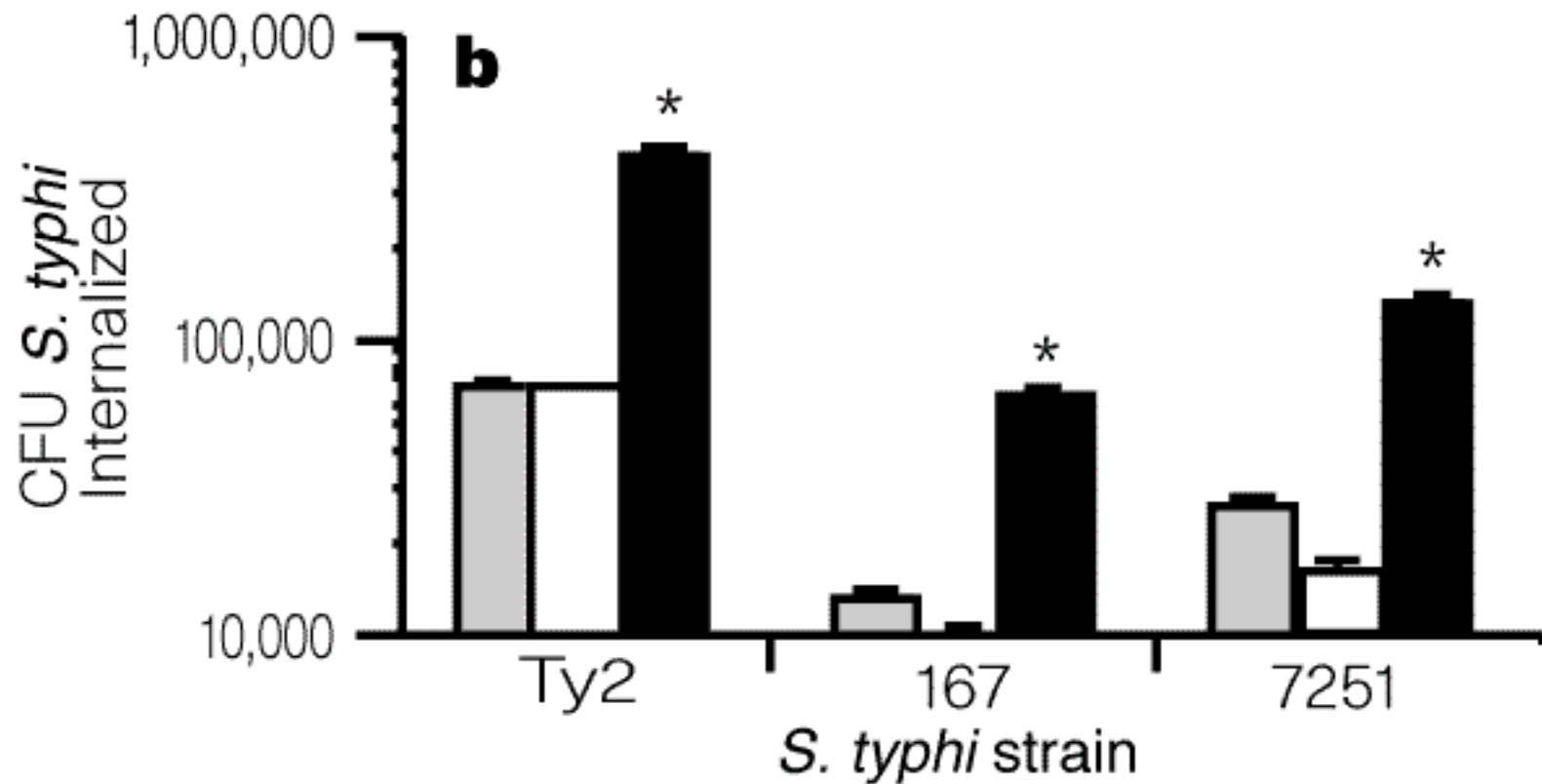
Michon et al, 2000, IAI, 68: 3164-71

HIV enters macrophages through the cytokine receptor CCR5



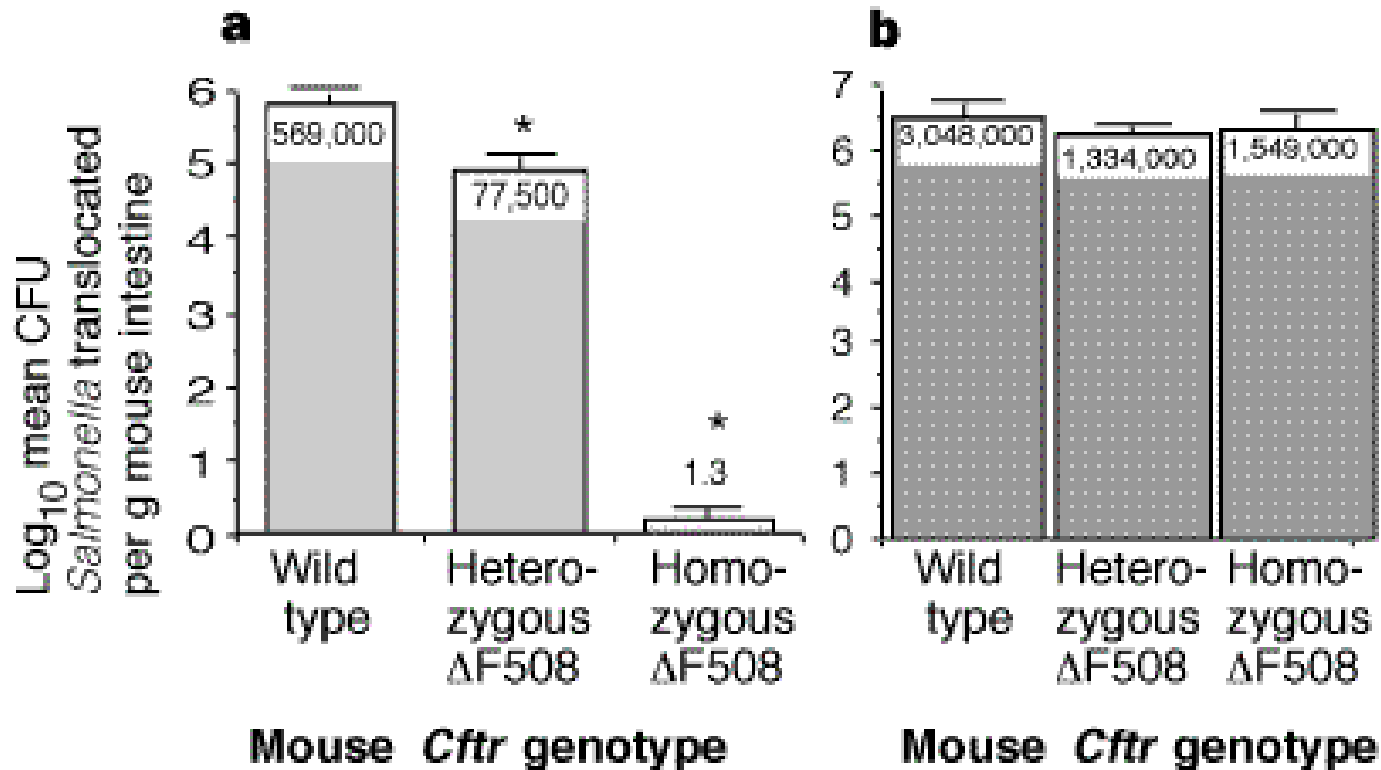
How can we use this information?

Cystic fibrosis gene CFTR is the receptor of *Salmonella typhi*



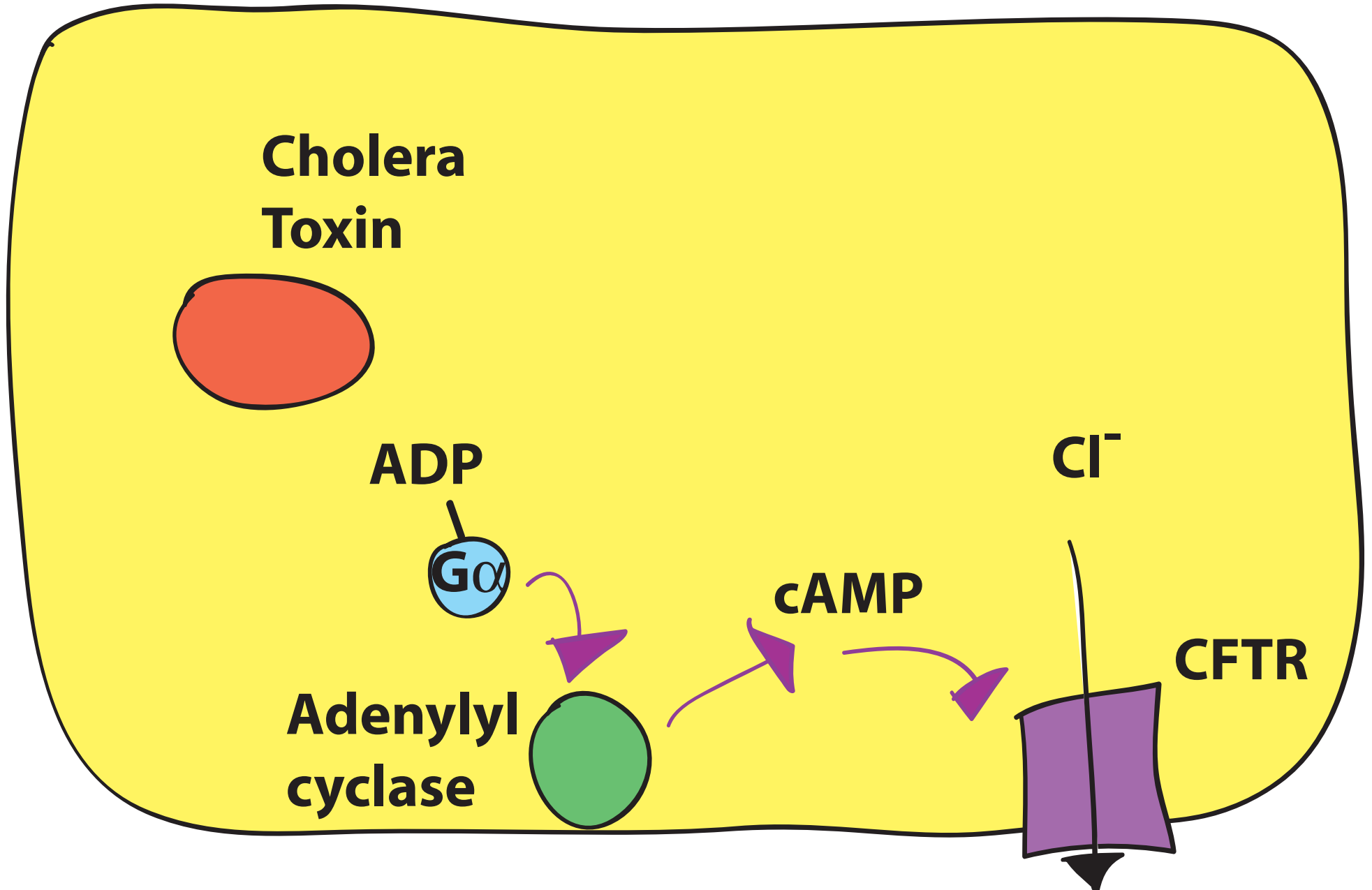
Pier et al. 1998, Nature 393: 79-82

CFTR mutant mice are resistant to some strains of *S.typhi*

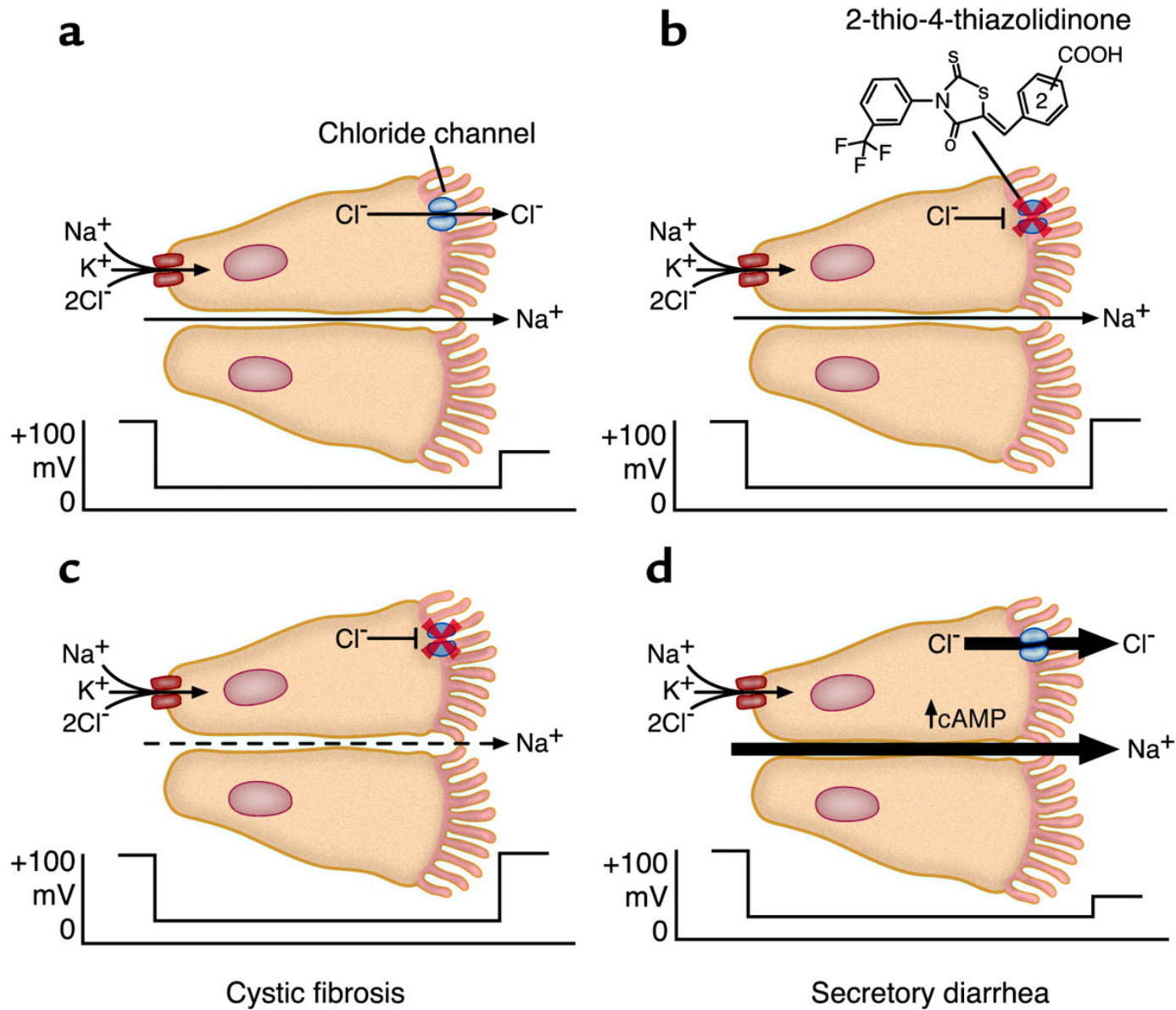


Pier et al. 1998, Nature 393: 79-82

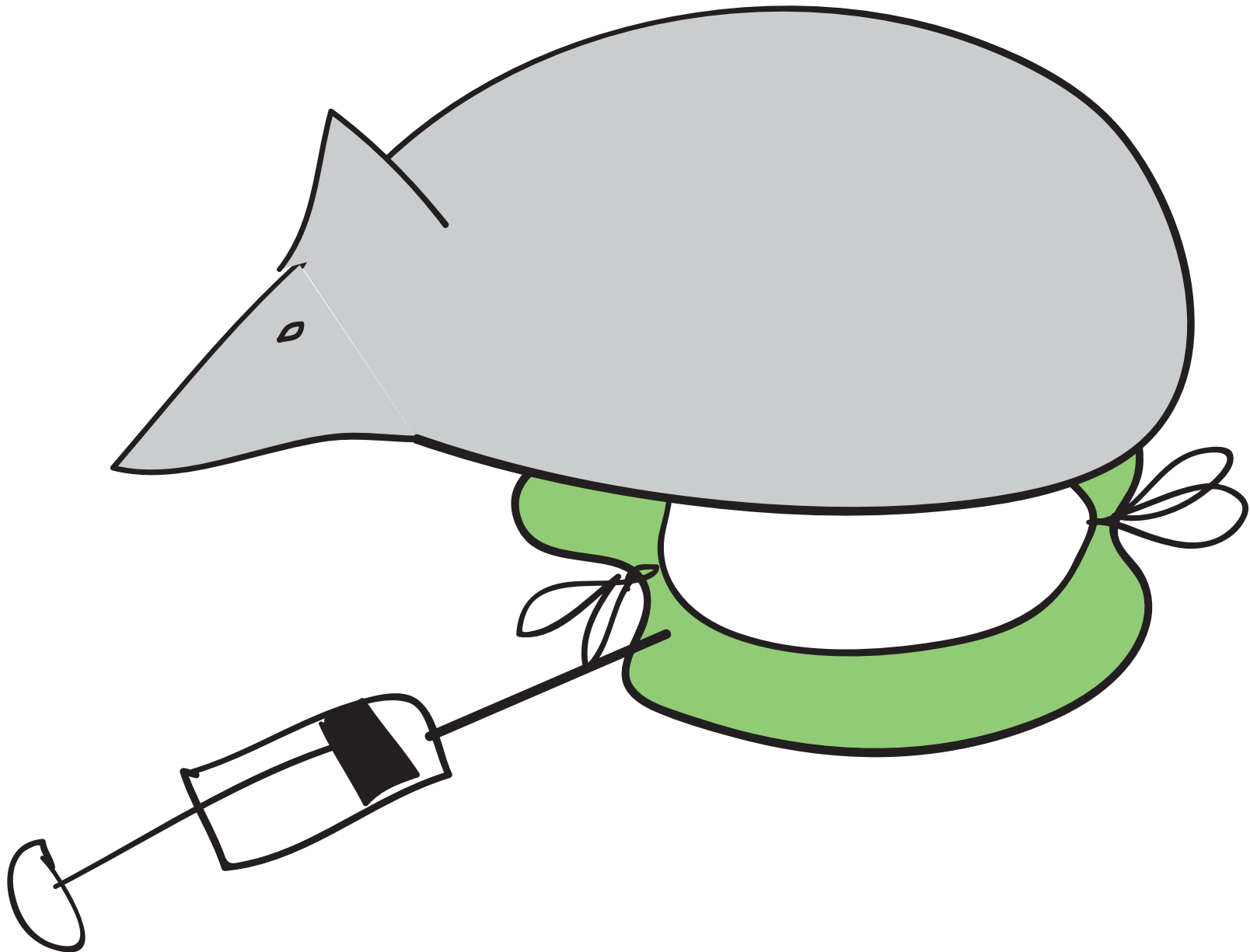
Cholera toxin and CFTR hypothesis



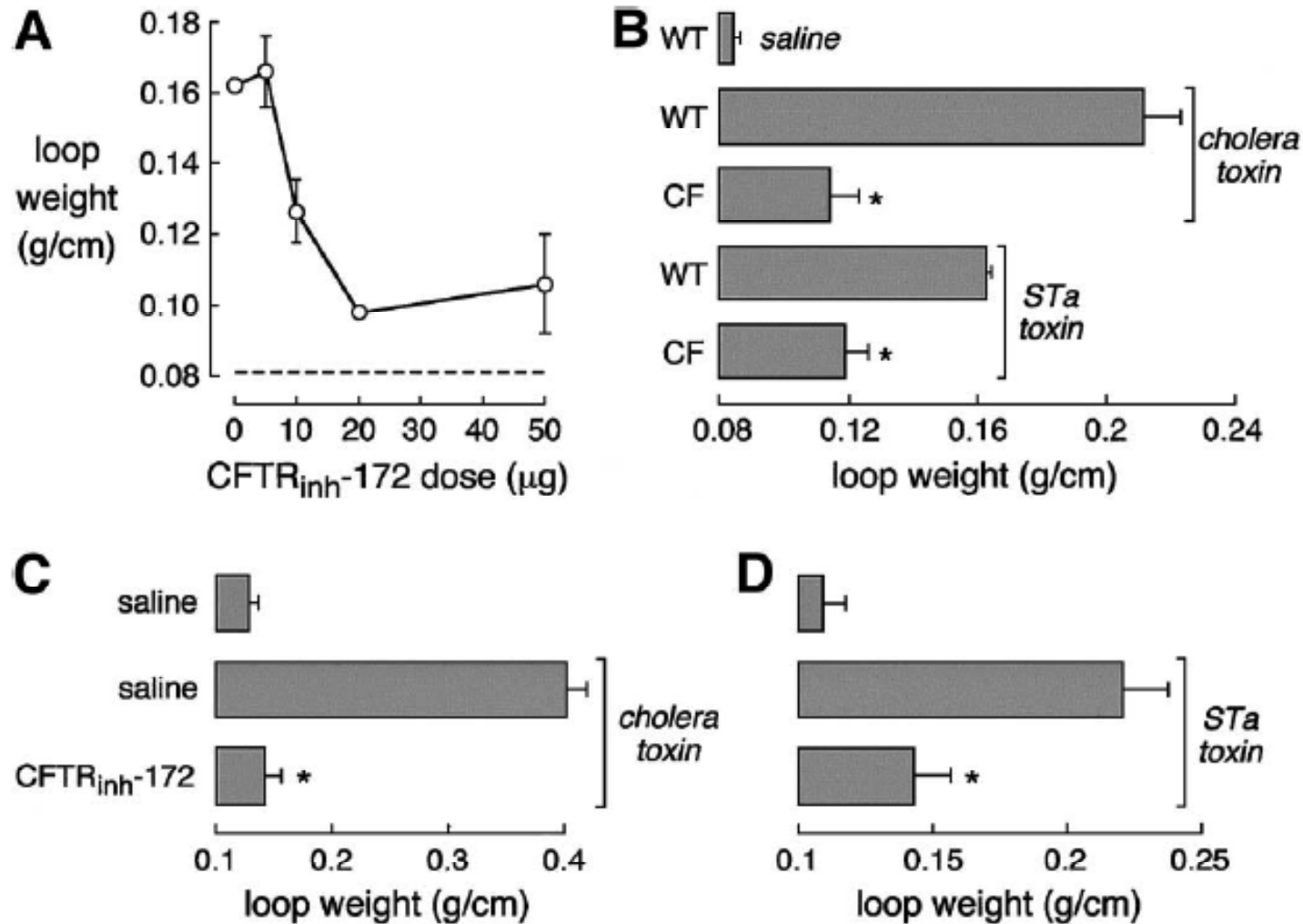
Cystic Fibrosis and Cholera



Gut loop experiment: toxin is injected into a closed loop of gut



Inhibition of the CFTR results in lowered volumes of diarrhea



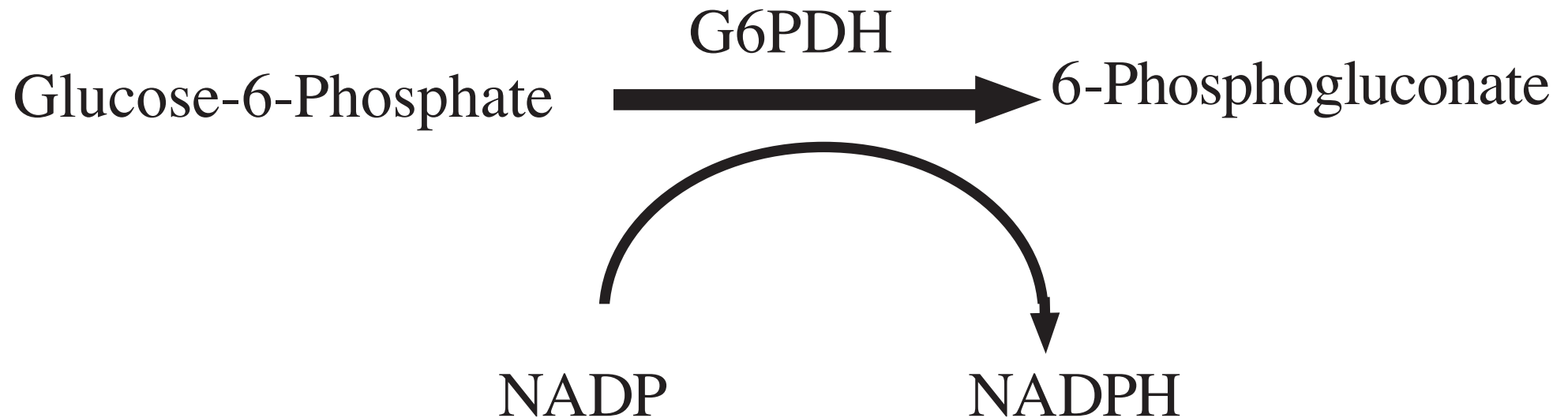
Thiagarajah et al. 2004, *Gastroenterology*, 126: 511-519

G6PDH carriers are less susceptible to severe malaria

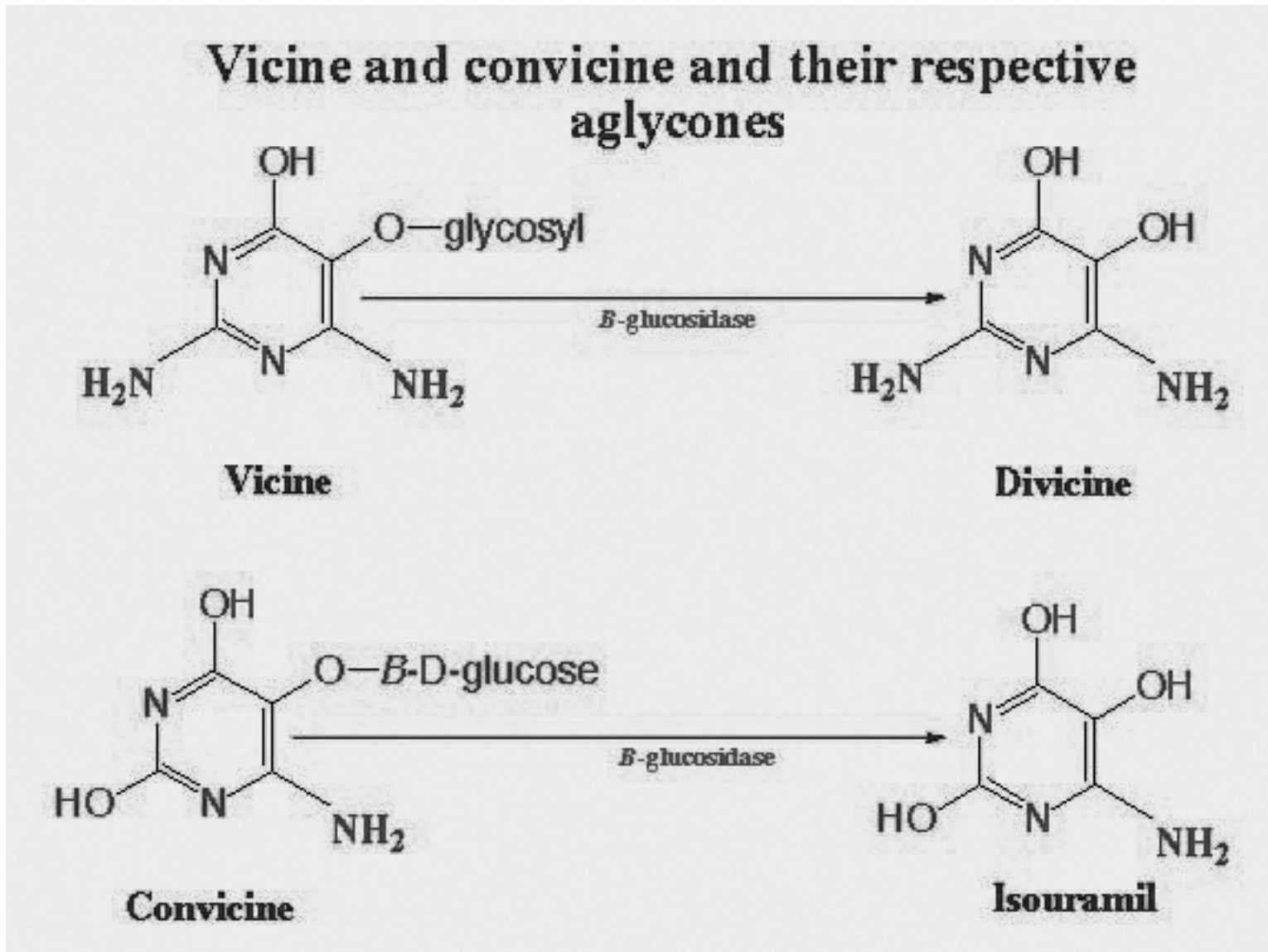
	Controls	Mild malaria	Severe malarial anaemia	Cerebral malaria	All severe malaria	Odds ratio (confidence interval), mild v. controls <i>P</i>	Odds ratio (confidence interval), severe v. controls <i>P</i>
Females heterozygotes							
Gambia	13.7 <i>n</i> = 182	9.1 <i>n</i> = 165	5.3 <i>n</i> = 94	6.8 <i>n</i> = 174	6.7 <i>n</i> = 255	0.62 (0.30–1.29) <i>P</i> = 0.23	0.45 (0.22–0.89) <i>P</i> = 0.02
Kenya	27.3 <i>n</i> = 143	17.2 <i>n</i> = 116	20.6 <i>n</i> = 68	16.9 <i>n</i> = 65	18.8 <i>n</i> = 133	0.52 (0.27–0.99) <i>P</i> = 0.047	0.60 (0.33–1.11) <i>P</i> = 0.11
Combined odds ratio						0.59 (0.36–0.94) <i>P</i> = 0.027	0.54 (0.34–0.84) <i>P</i> = 0.006
Male hemizygotes							
Gambia	5.9 <i>n</i> = 239	2.7 <i>n</i> = 182	1.3 <i>n</i> = 80	1.9 <i>n</i> = 208	1.4 <i>n</i> = 279	0.45 (0.14–1.38) <i>P</i> = 0.20	0.23 (0.06–0.77) <i>P</i> = 0.012
Kenya	18.8 <i>n</i> = 149	14.3 <i>n</i> = 133	14.9 <i>n</i> = 47	8.6 <i>n</i> = 70	11.1 <i>n</i> = 117	0.72 (0.23–1.42) <i>P</i> = 0.40	0.54 (0.25–1.15) <i>P</i> = 0.12
Combined odds ratio						0.63 (0.36–1.11) <i>P</i> = 0.12	0.42 (0.22–0.77) <i>P</i> = 0.004

Ruwende et al. 1995, Nature 376

G6PDH: source of NADPH in the body

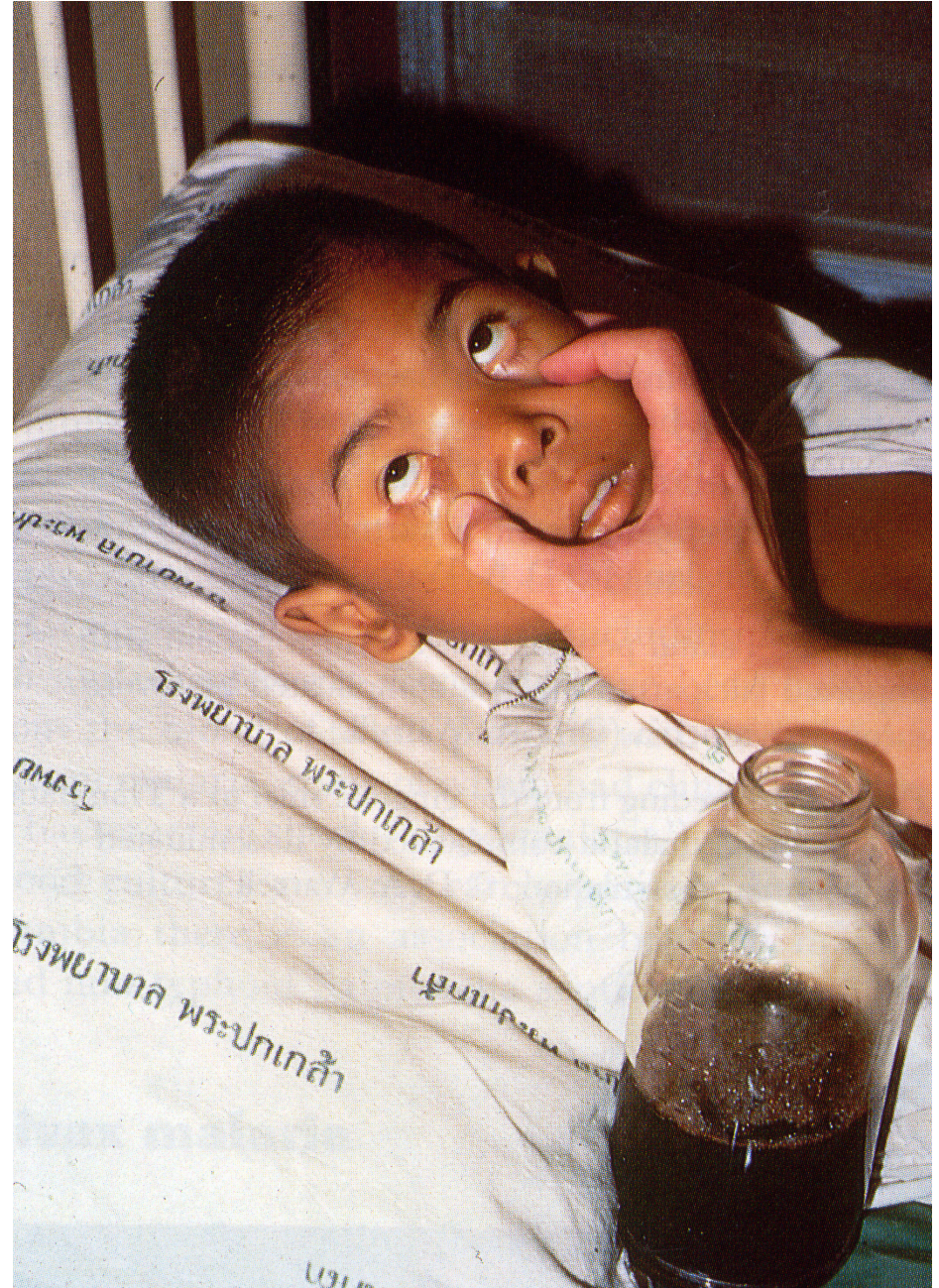


G6PDH homozygotes are sensitive to oxidizing reagents



Two compounds found in fava beans that are toxic to homozygotes

G6PDH combined with malaria and oxidant drugs causes “blackwater fever”



Why are fava beans, G6PDH and malaria associated?



■ malaria ■ G6PD deficiency + malaria ■ fava beans + malaria
■ fava beans ■ all features ■ G6PD deficiency + fava beans

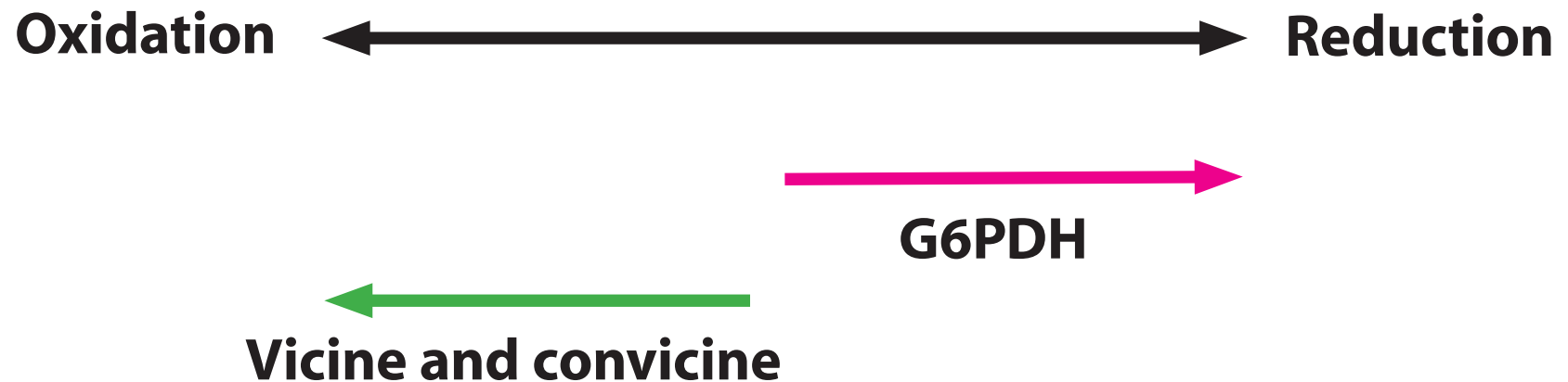
<http://www.as.ua.edu/ant/bindon/ant475/g6pd/g6pd.htm>

Plasmodium is more sensitive to oxidants in G6PDH mutants

System	- β -glucosidase	+ β -glucosidase
Normal RBC + vicine	1.17 \pm 0.103	1.00 \pm 0.053
Normal RBC + convicine	0.83 \pm 0.052	0.74 \pm 0.028
Hemizygous G6PD ⁻ + vicine	1.13 \pm 0.065	0.76 \pm 0.043
Hemizygous G6PD ⁻ + convicine	0.59 \pm 0.017	0.44 \pm 0.033
Homozygous G6PD ⁻ + vicine	0.60 \pm 0.172	0.33 \pm 0.103

Ginsberg et al. 1996, Parasitology 113: 7-18

Fava beans and G6PDH deficiency alter the ability of the cell to deal with oxidative stress



Plasmodium is sensitive to oxidative stress