

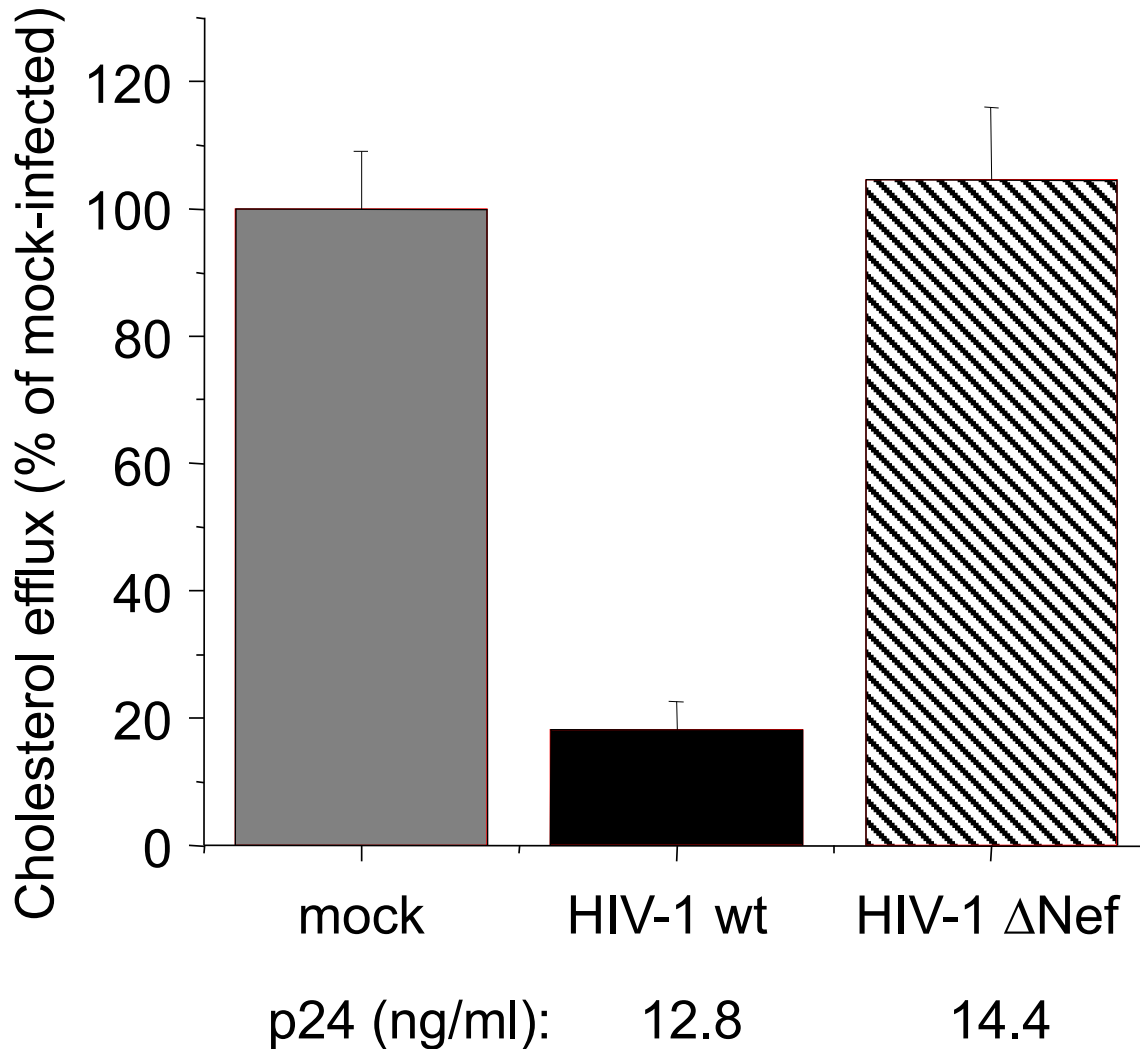
HIV and atherosclerosis: an unexpected connection

Michael Bukrinsky

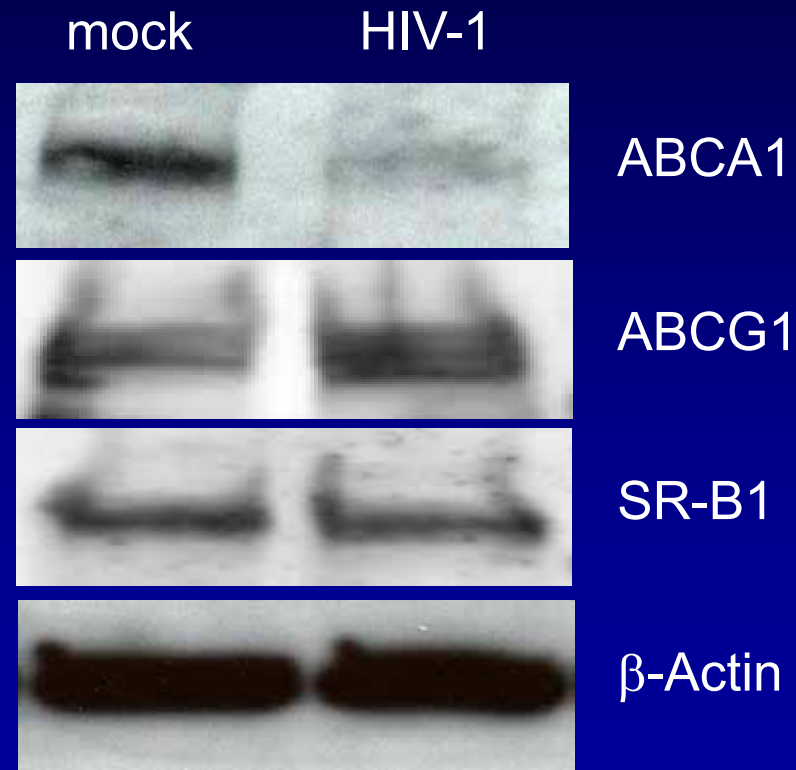
The George Washington University School of Medicine and
Health Sciences



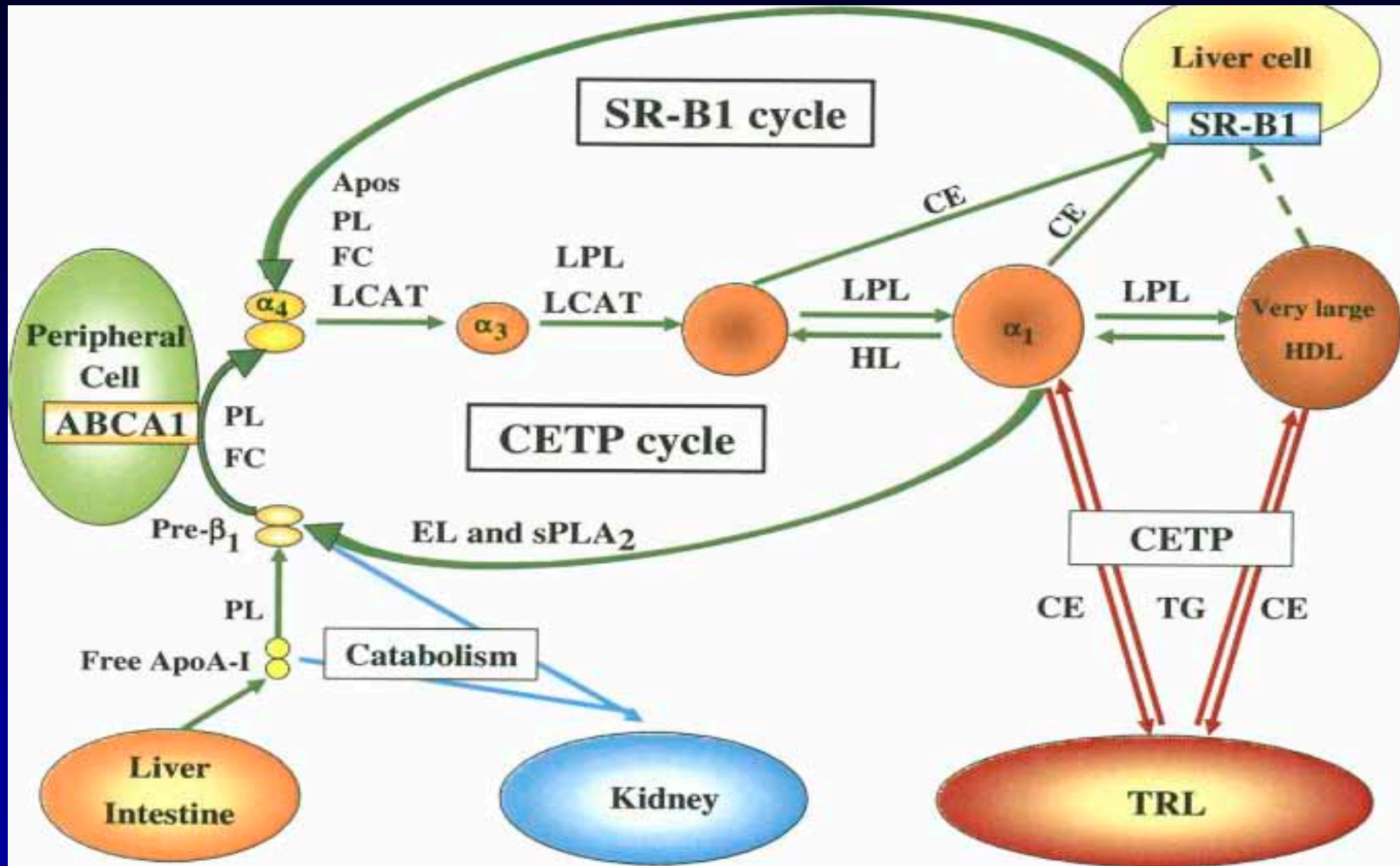
Nef-dependent HIV-mediated impairment of cholesterol efflux from macrophages



Specific Down-Modulation of ABCA1 in HIV-Infected Macrophages



A model of HDL particle metabolism

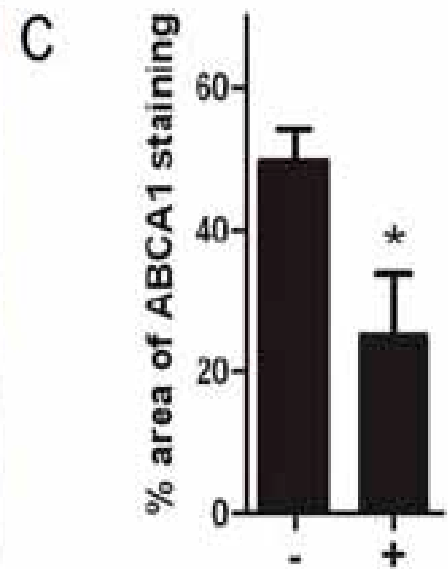
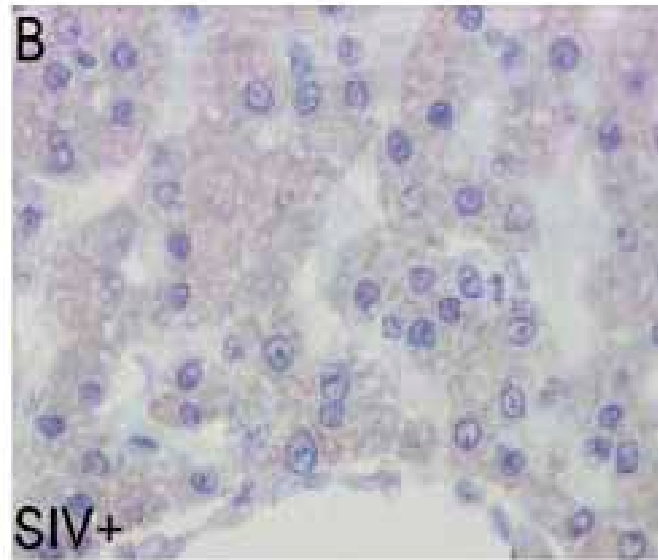
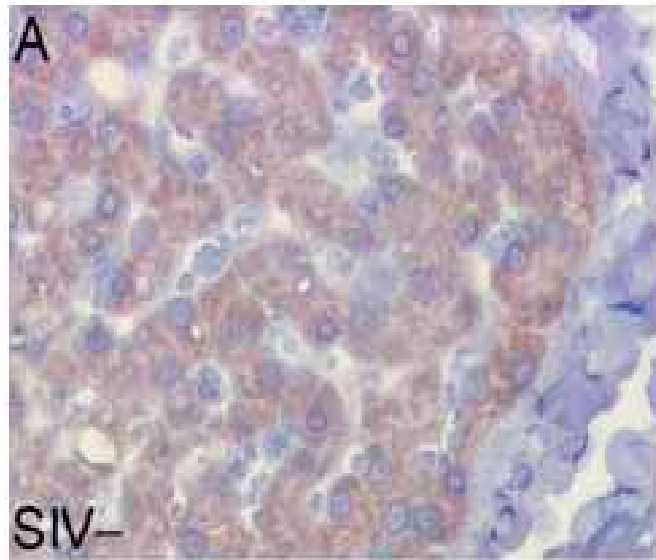


HDL analysis on serum samples from SIV-infected macaques

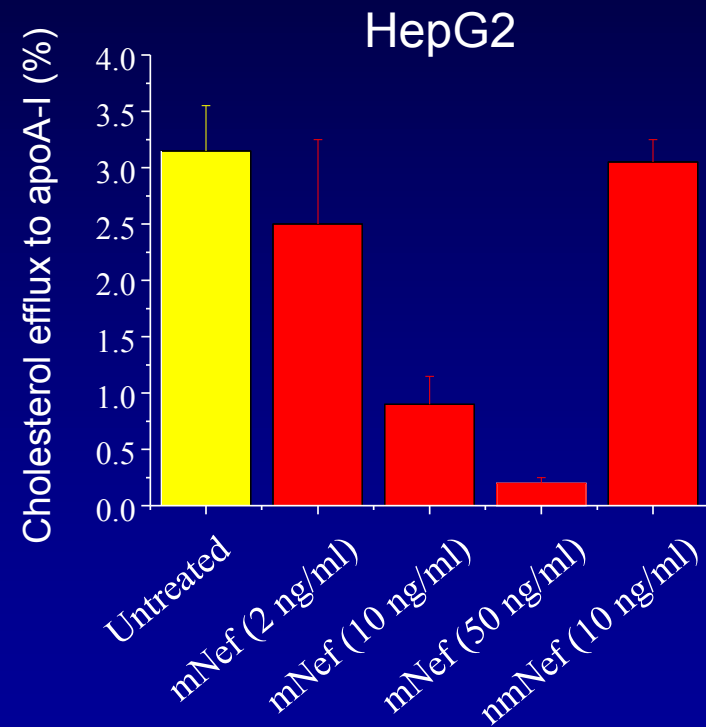
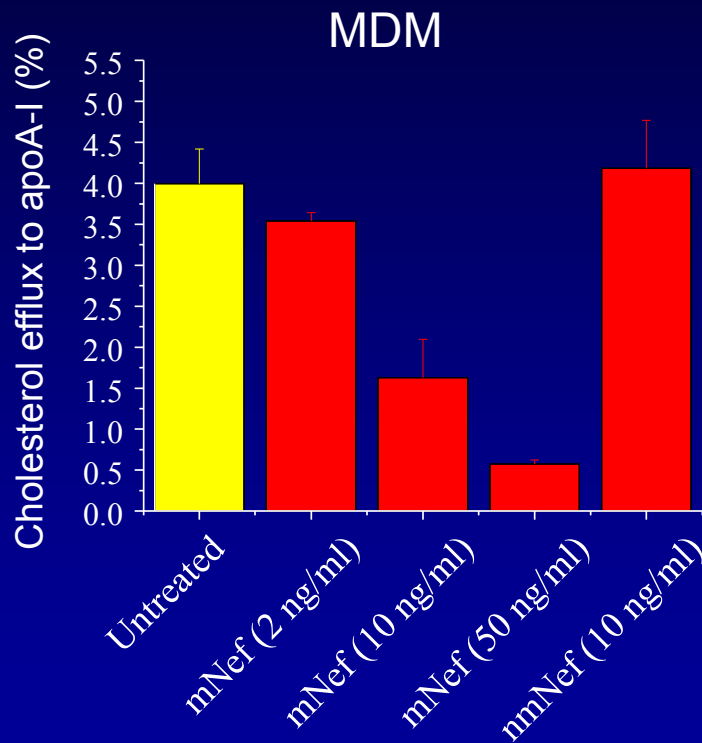
HDL particle	ND (n=7)	AD (n=7)	AD SIV (n=8)	ANOVA p value	Post test comparison		
					ND vs AD	AD vs AD SIV	ND vs AD SIV
Pre β -1a	20.72	31.10	37.08	0.003*			<0.05 (\uparrow)**
Pre β -1b	6.98	7.89	15.75	0.009†			<0.05 (\uparrow)‡
VL- α	17.74	6.65	8.20	0.015*	<0.05 (\downarrow)**		<0.05 (\downarrow)**
α -1	17.37	9.29	7.07	<0.001*	<0.05 (\downarrow)**		<0.05 (\downarrow)**
α -2	10.97	11.69	10.11	0.489*			
α -3	8.75	13.51	8.92	0.002*	<0.05 (\uparrow)**	<0.05 (\downarrow)**	
α -4	6.89	8.56	5.18	0.012*		<0.05 (\downarrow)**	

Values are mean \pm SD (in milligrams per deciliter). *One way analysis of variance; †Kruskal-Wallis one way analysis of variance on ranks; **Tukey post test comparison or ‡ Dunn's method

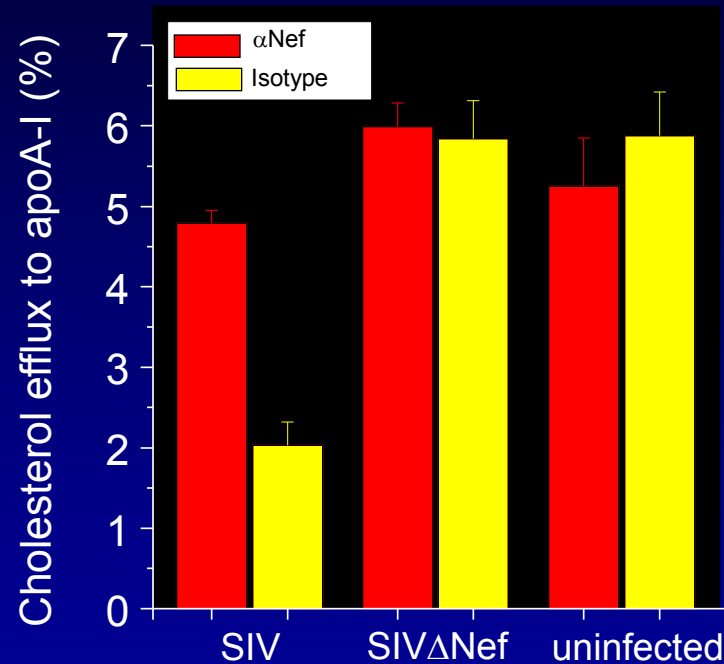
ABCA1 is downregulated in liver of SIV-infected macaques



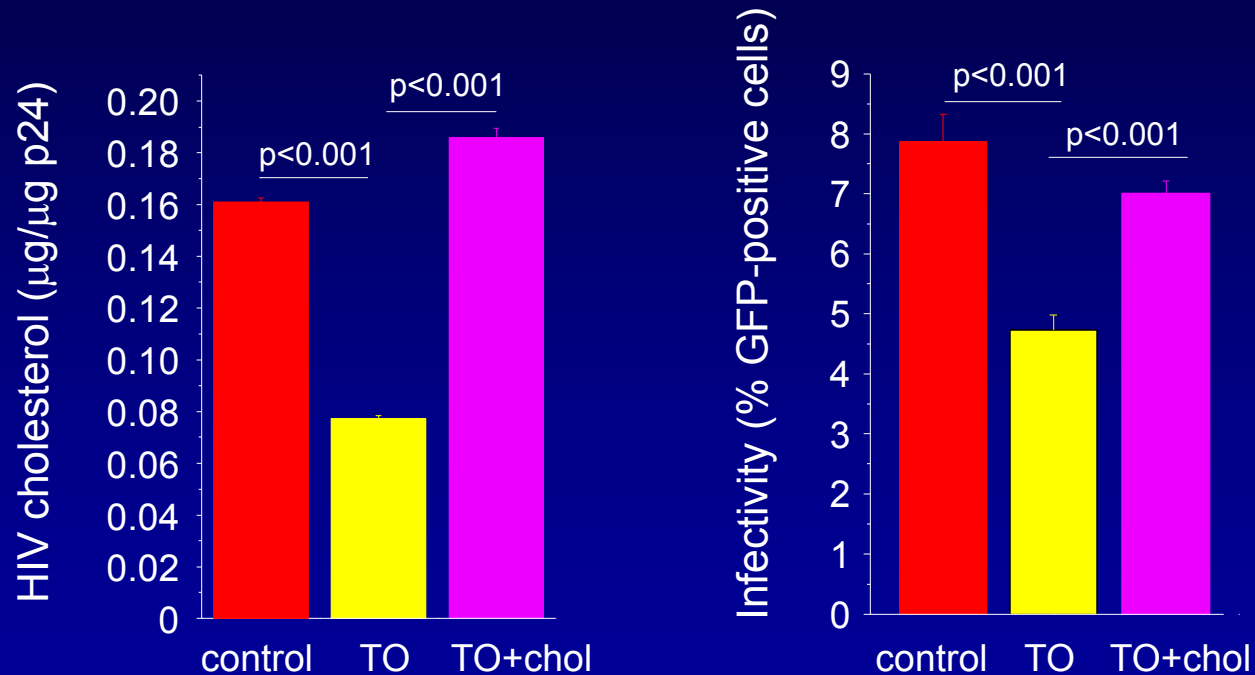
Recombinant myristoylated Nef suppresses cholesterol efflux



Suppression of cholesterol efflux by Nef in the sera from SIV-infected macaques

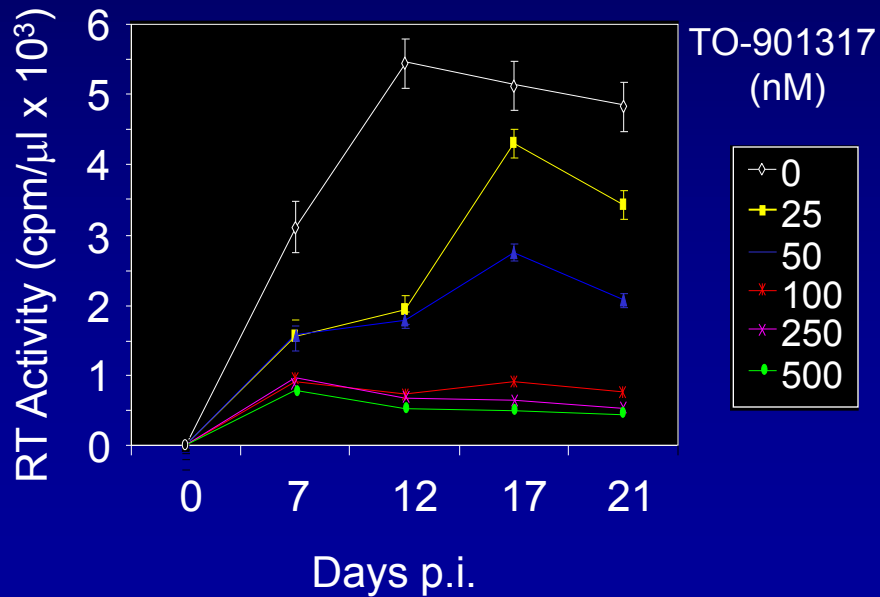


TO-901317 reduces viral cholesterol and infectivity

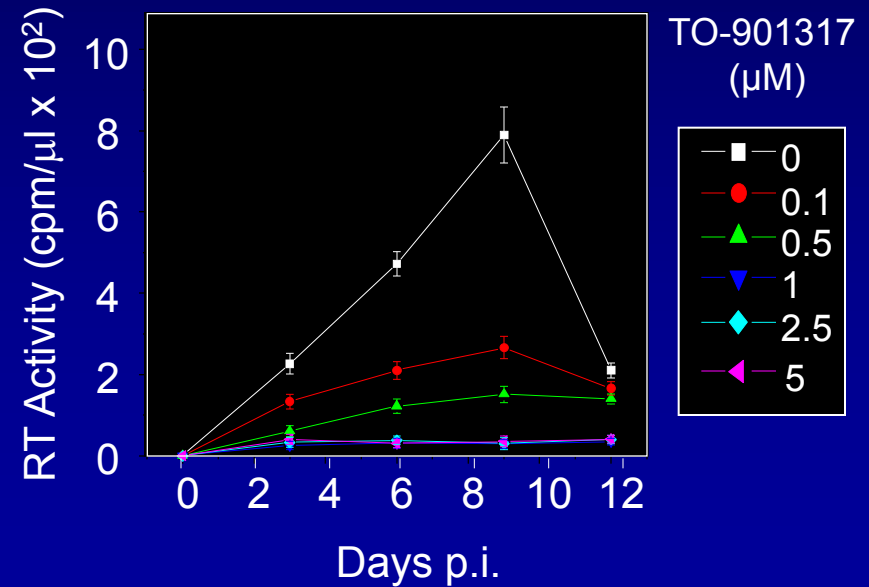


TO-901317 inhibits HIV-1 replication in vitro

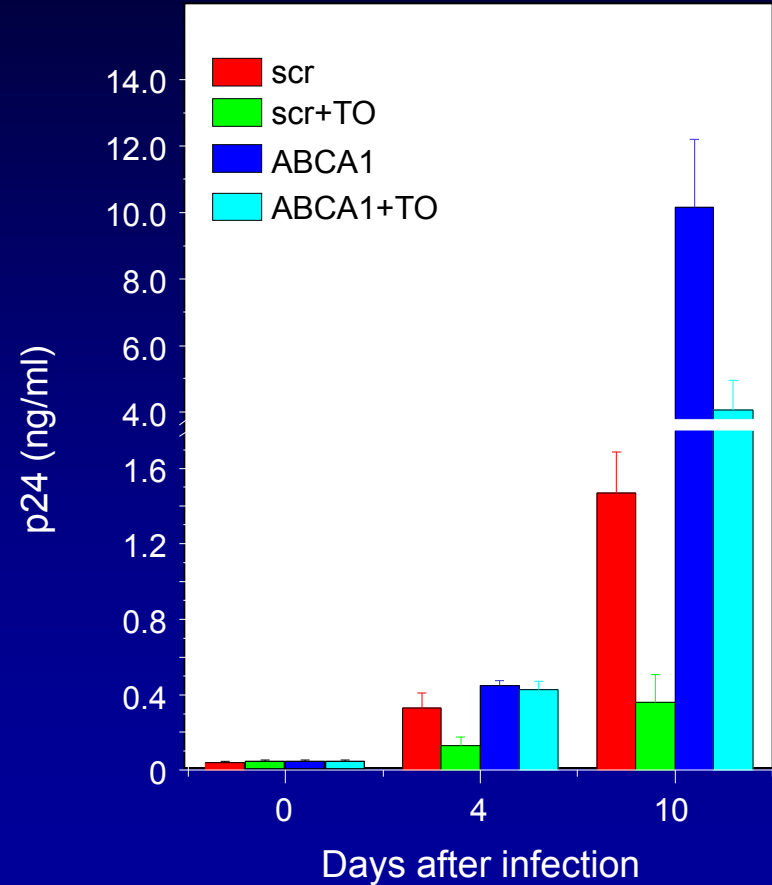
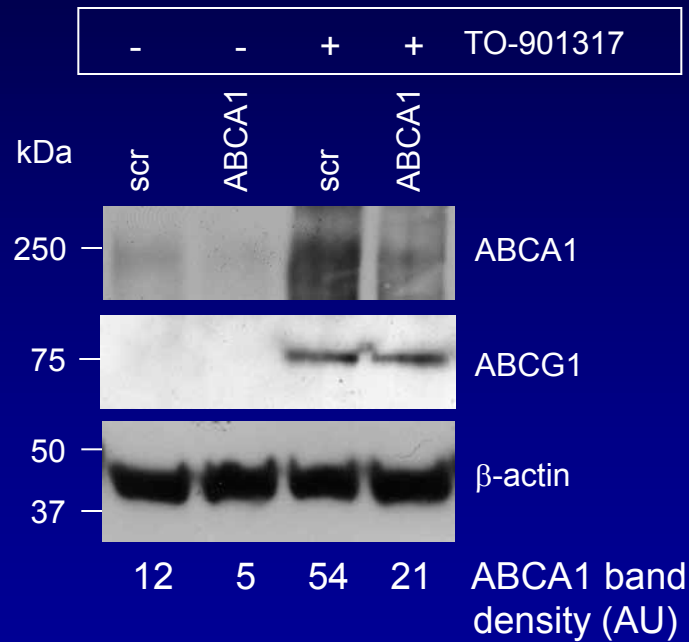
MDM



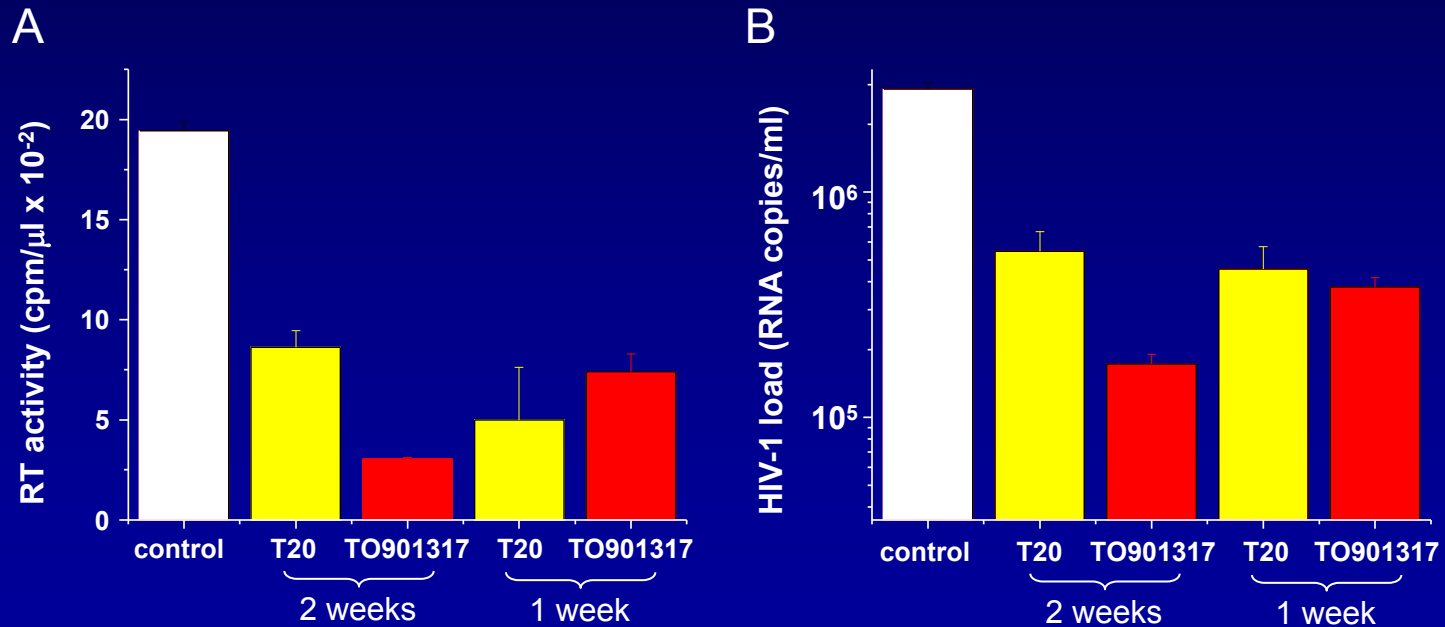
CD4+ T cells



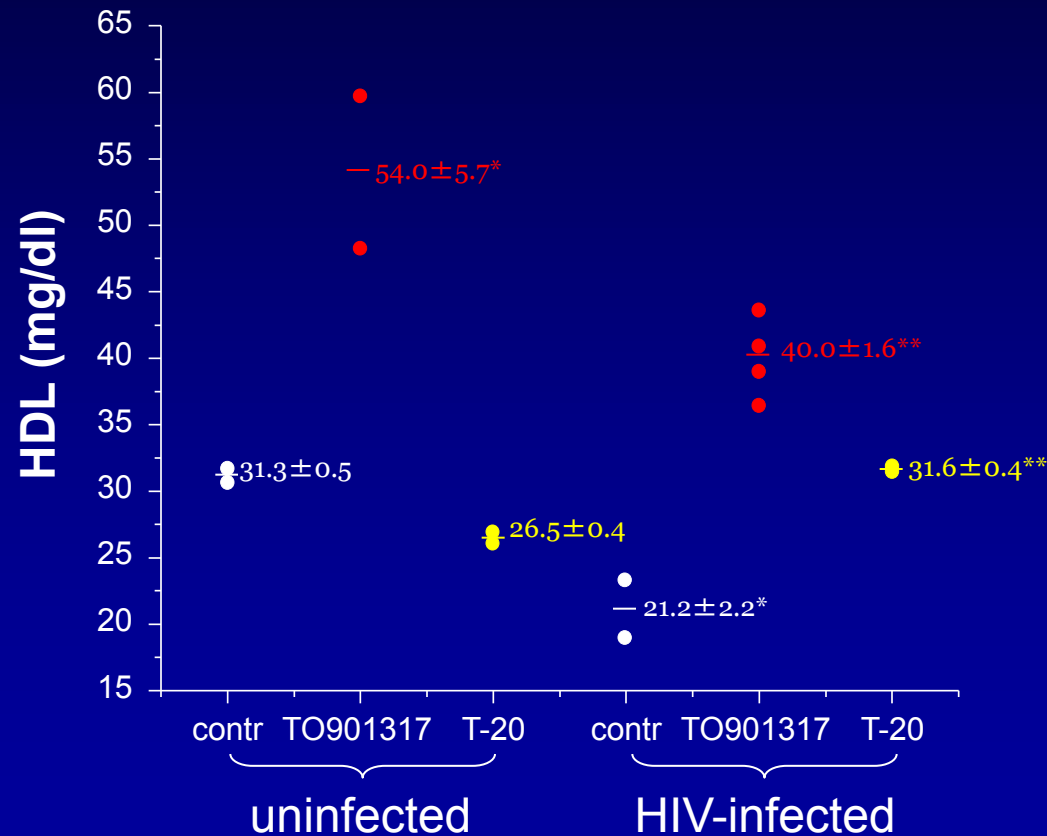
Anti-HIV activity of TO-901317 depends on ABCA1

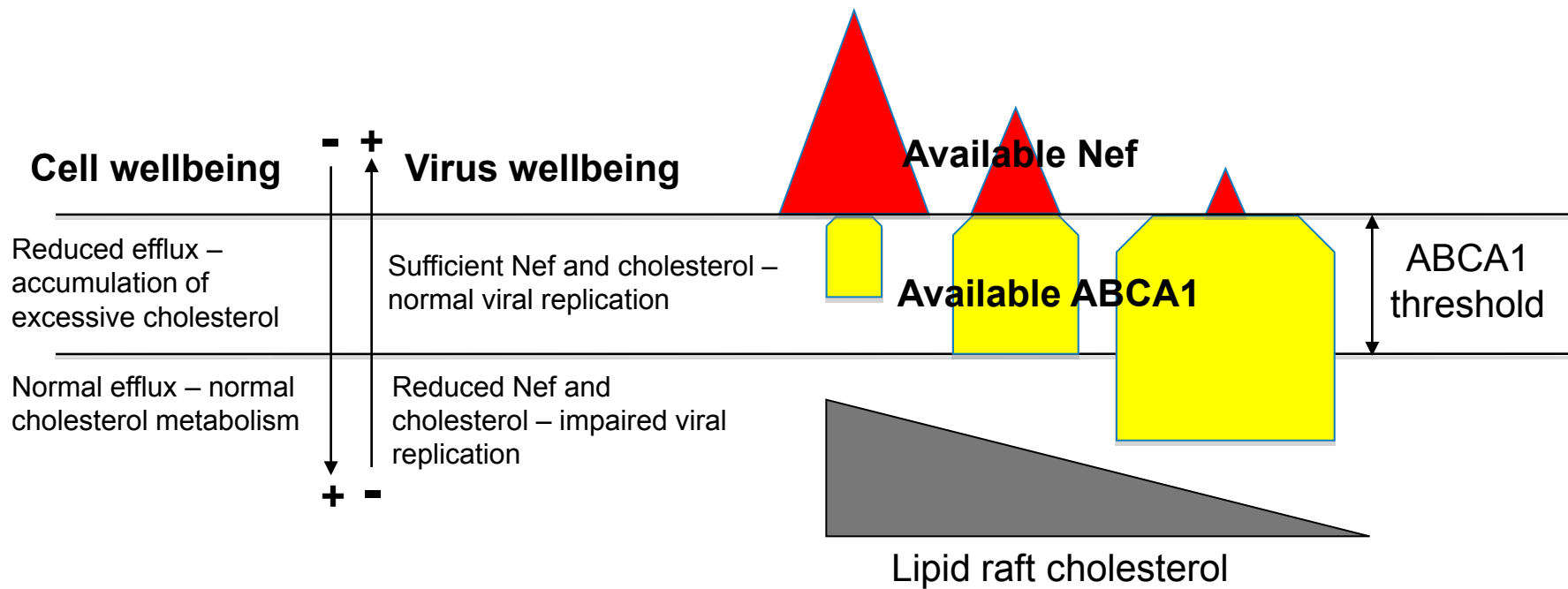


LXR agonist TO901317 suppresses HIV-1 replication in humanized mice

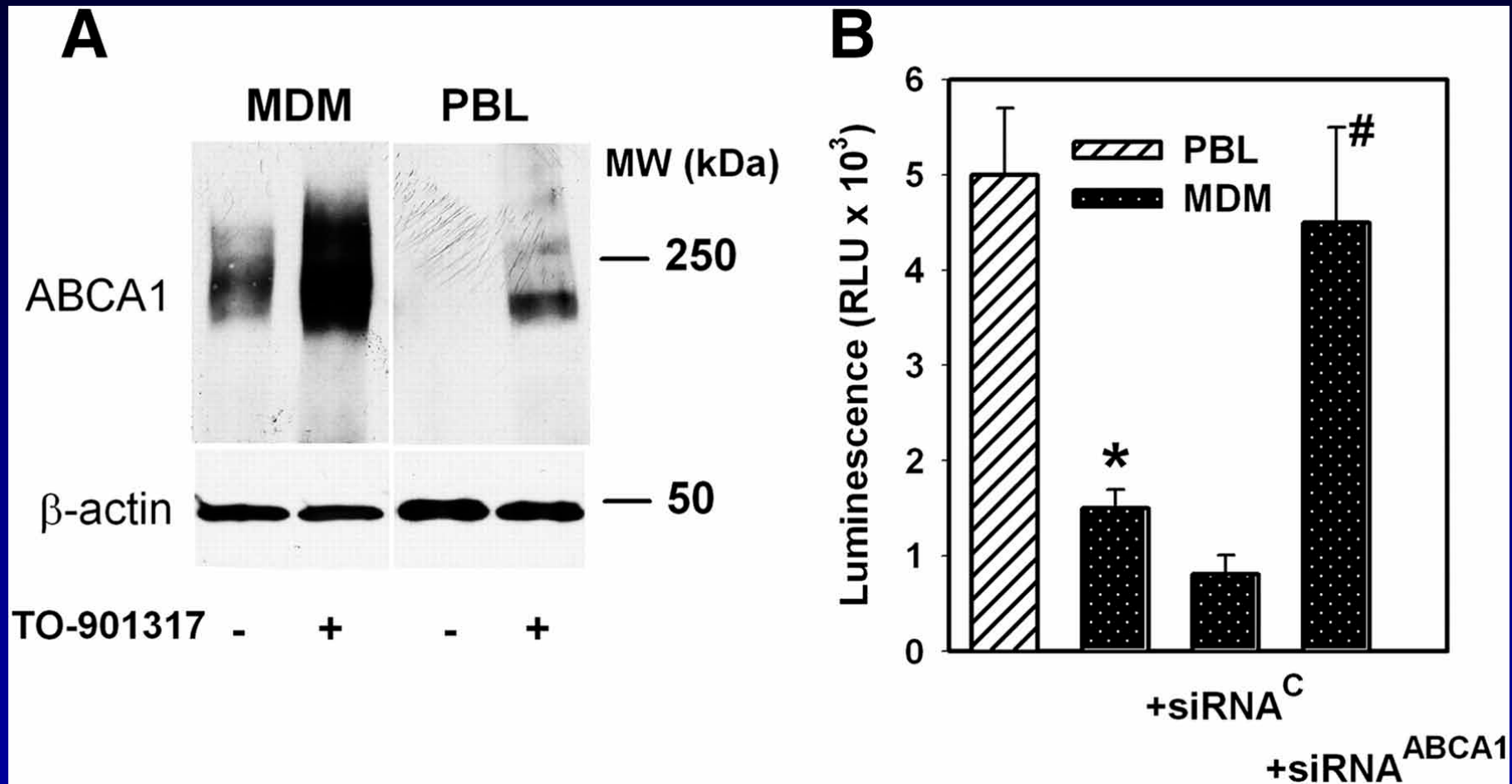


LXR agonist TO901317 reverses HIV-induced downregulation of HDL





HIV-1 infectivity correlates with ABCA1 expression in producer cells



Conclusions:

- HIV infection impairs cholesterol efflux and reduces HDL levels in plasma
- Nef is responsible for these effects through inhibition of ABCA1 activity
- Nef released into the bloodstream induces systemic inhibition of reverse cholesterol transport evidenced by HDL remodelling

Conclusions:

- HIV infectivity critically depends on virus's ability to impair cholesterol efflux
- Nef and ABCA1 are in constant antagonistic interactions in HIV-infected cells: high levels of Nef inhibit cholesterol efflux, whereas high expression of ABCA1 reduces HIV infectivity
- Anti-HIV effect of LXR agonist is mediated by stimulation of ABCA1 expression
- LXR agonist reduces cholesterol in lipid rafts and in the virions
- LXR agonist reduces HIV production and inhibits HIV infectivity
- Drugs stimulating expression of ABCA1 and cholesterol efflux may have a dual beneficial effect: anti-atherosclerotic and anti-HIV

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NATION HOUSE OF CHAD. ILLINOIS

THE TEST OF OUR PROGRESS
IS NOT WHETHER WE ADD MORE
TO THE ABUNDANCE OF THOSE
WHO HAVE MUCH, IT IS WHETHER
WE PROVIDE ENOUGH FOR
THOSE WHO HAVE TOO LITTLE.

