

#295 INHIBITION OF P2X7 ENHANCES T-CELL POTENTIAL OF CD34+ IN HIV+ c-ART NONRESPONDERS



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1. INTRODUCTION

Even with long-term viral suppression by c-ART, peripheral CD4+ T-cell levels are not fully restored in a significant proportion of HIV+ individuals. These immunological non-responders (INRs) have a higher risk of developing AIDS and non-AIDS events and a lower life expectancy than the general population. The mechanisms underlying this poor recovery are not fully understood. **We hypothesize that impaired T-cell differentiation from CD34+ hematopoietic progenitors could, at least partially, explain low CD4+ levels in treated HIV+ patients.**

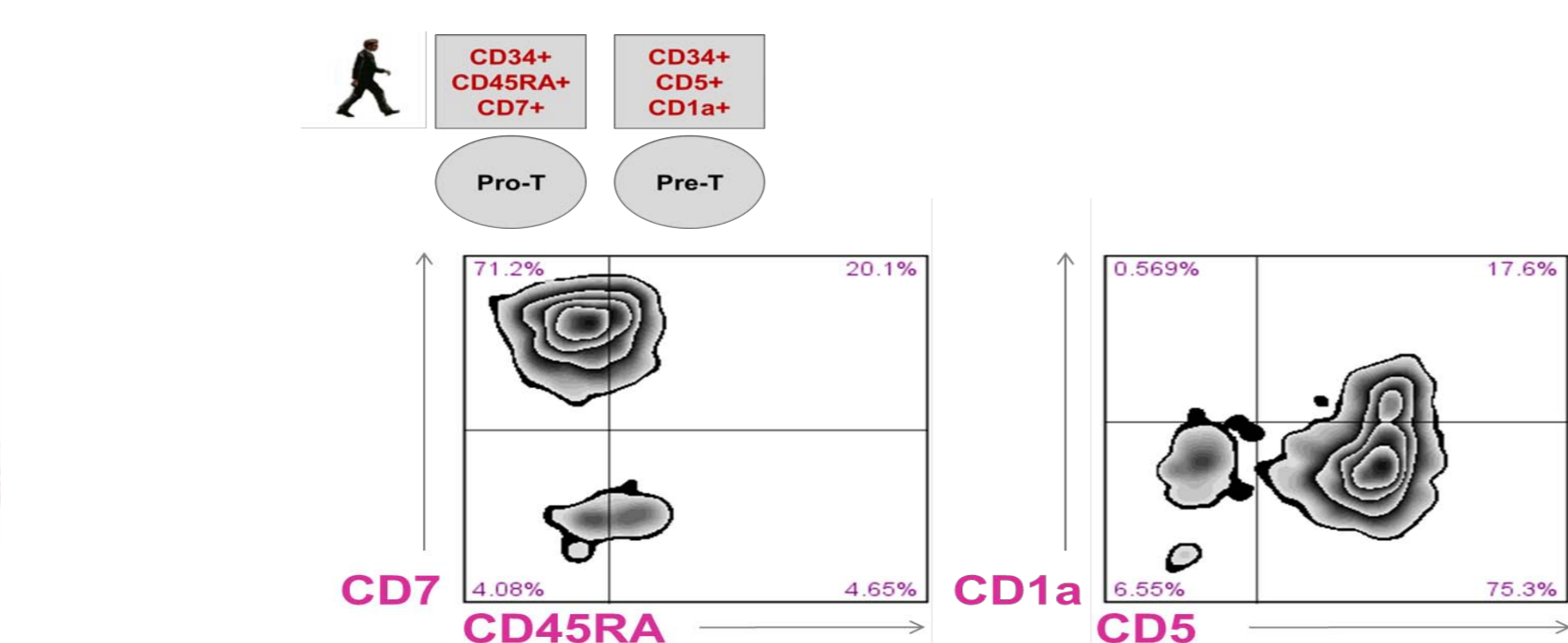
2. IMPAIRED LYMPHOPOIESIS IN HIV+ INRs

Characteristic	HIV-	HIV+ IR	HIV+ INR	P		
				HIV- vs IR	IR vs INR	HIV- vs INR
Number	18	16	16			
Age (year)	47.5 (34-55.25)	46 (40.25-52.75)	53 (47-63)	NS	NS	NS
Sex ratio, F/M	0.21	0.5	0.8	NS	NS	NS
Infection duration (years)	-	10 (7.5-18.75)	13 (8-17)		NS	
Treatment duration (years)	-	9.5 (7.25-14.75)	13 (8-16)		NS	
CD4 nadir (cells/mm ³)	-	191 (103-261)	102 (48-197)		NS	
CD4 absolute count (cells/mm ³)	NA	1086 (927-1194)	379.5 (280.3-431)		****	
CD8 absolute count (cells/mm ³)	NA	644.5 (568.5-798.5)	621 (492.5-808.8)		NS	
CD4/CD8 ratio	2.31 (1.8-3.02)	1.69 (1.39-1.86)	0.58 (0.48-0.77)	***	****	****
Reservoir (log ₁₀ DNA copies/mL of plasma)	-	3.25 (2.65-3.4)	3.15 (2.75-3.36)		NS	
CD4+ RTE, %	28 (24.75-33.35)	24.3 (16.7-29.05)	8.61 (5.46-17.65)	NS	*	**
CD34+, %	0.07 (0.03-0.14)	0.05 (0.03-0.11)	0.07 (0.03-0.14)	NS	NS	NS

3. SPECIFIC ALTERATION OF T-CELL POTENTIAL IN INRs

Limiting dilution analysis (LDA)

CD34+ cells (purity >97%)
OP9-huDelta1 murine stroma



Dose: 10, 50, 100 cells/well

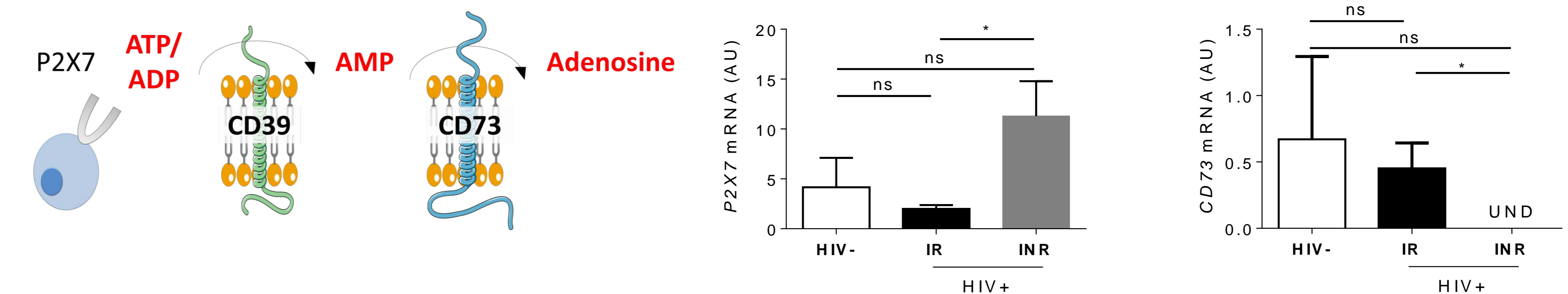
Replicates: 32, 48 ou 96 wells/condition

Response: T cells precursors (CD5+1a+) at D21

	HIV-	HIV+ IR	HIV+ INR	P		
				HIV- vs IR	IR vs INR	HIV- vs INR
T-cell potential	71.9 (54.8-94.5)	86.3 (67.3-111)	240.6 (162.1-806.6)	NS	***	**
B-cell potential	63.1 (42.5-94.1)	47 (32.5-68.2)	64 (42.04-100.1)	NS	NS	NS

4. INCREASED CELL DEATH IN CD34+ FROM INRs

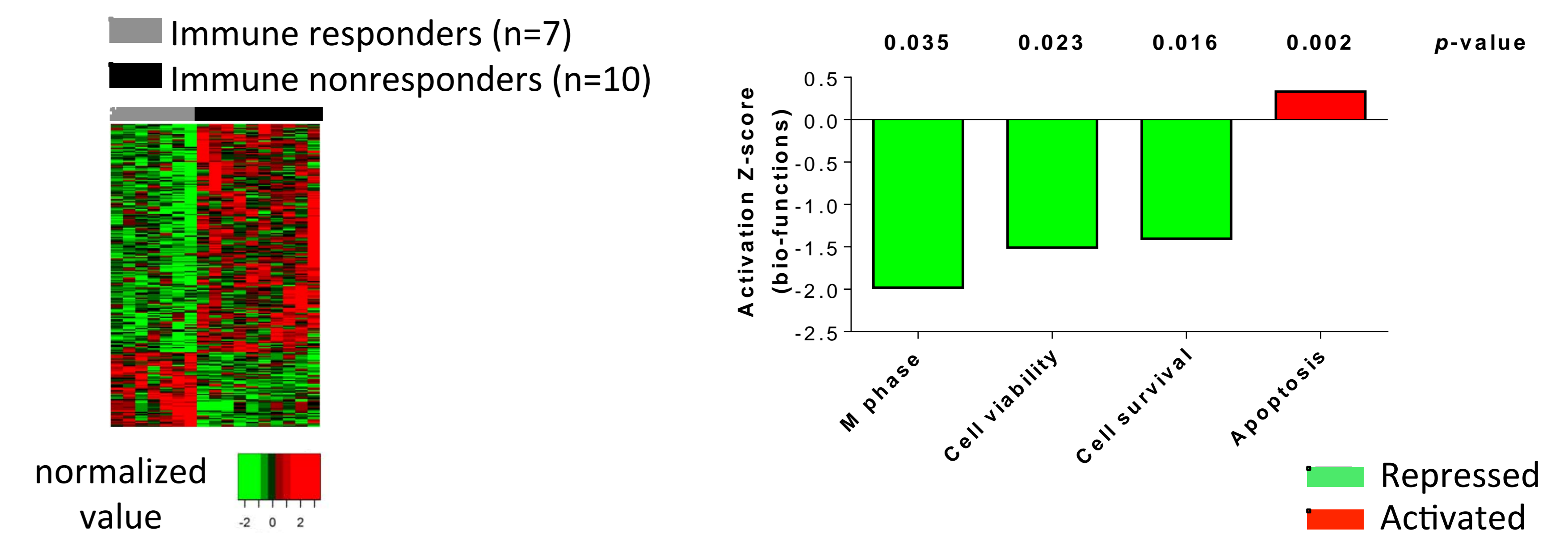
1. Increased P2X7 and absence of CD73 expression in CD34+ from INR :



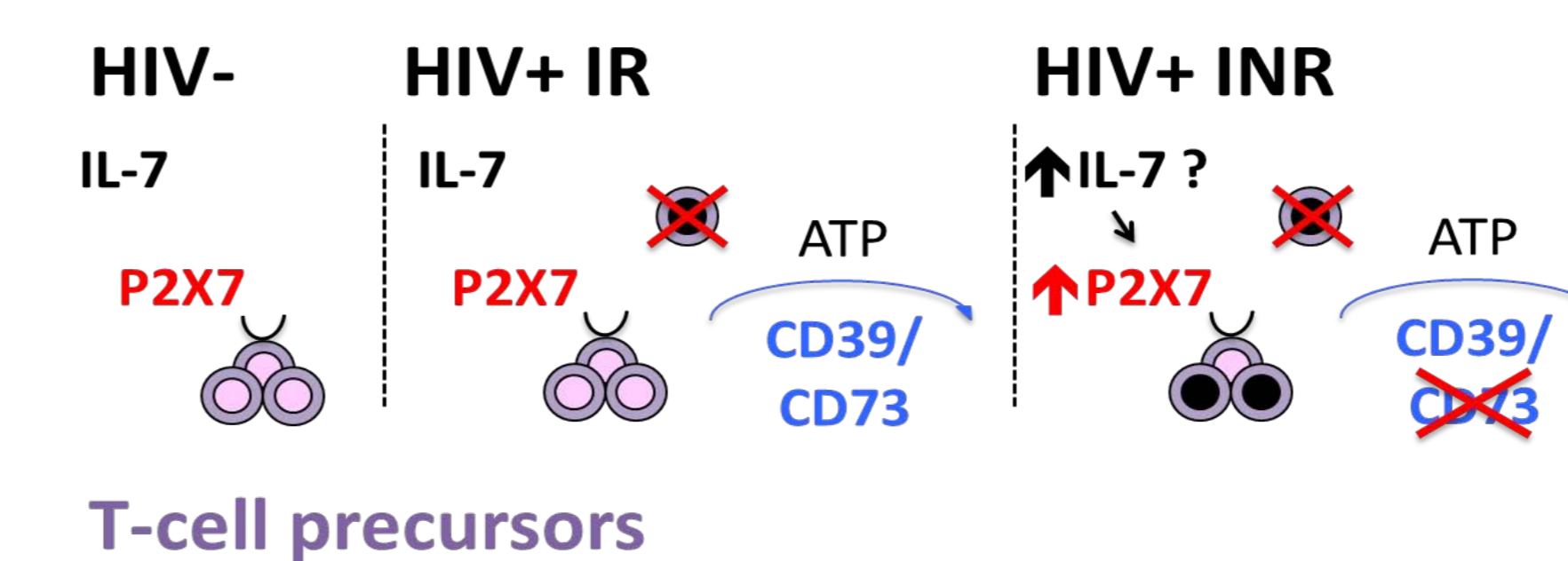
2. P2X7 antagonist, PPAD, restores T-cell differentiation potential of CD34+ from INRs:

T-cell potential	Cell frequency (1/)		P
	HIV+ INR mock	HIV+ INR PPAD	
	314.7 (186.3-532.3)	145.3 (98.3-214.7)	*

3. Downregulation of cell survival pathways and an upregulation of apoptosis in CD34+ cells from INRs



5. CONCLUSIONS



Our results suggest that strategies, such as anti-P2X7, might dramatically improve outcomes in c-ART treated HIV+ immune nonresponders.