



Presentation to RAC

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Question to be addressed

- Do results of a Phase 2 clinical study of JVRS-100 adjuvant 2ith TIV (Fluzone) impact the on-going study of JVRS-100 for treatment of AML?
 - Unexpectedly, JVRS-100 reduced the antibody (but not the T cell) response to TIV in a dose dependent manner
 - There were no safety concerns



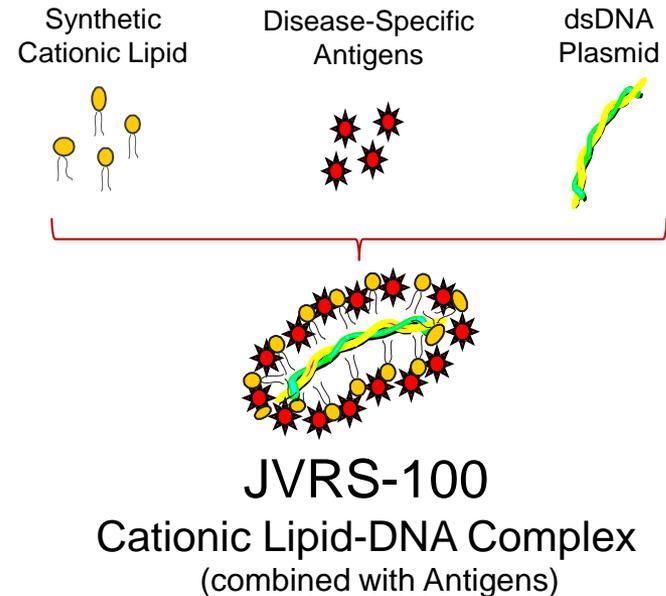
Agenda



- Brief review of Phase I JVRS-100 + Fluzone
- Interim Phase 2 data JVRS-100 + Fluzone
- Preliminary Phase 1 data JVRS-100 in AML
- Interpretation, discussion

JVRS-100 : A Novel Adjuvant

- Cationic lipid-DNA complex (CLDC)
 - Lipids: DOTIM (proprietary, non-toxic, metabolizable)+ synthetic cholesterol
 - DNA: *E coli* plasmid, non-coding, 4242bp, 288 CpG motifs
 - Lipids and DNA assemble by charge interactions
 - Ave. size 120 nm
 - Antigens non-covalently complex to CLDC



Ph 1 Seasonal Influenza Clinical Study

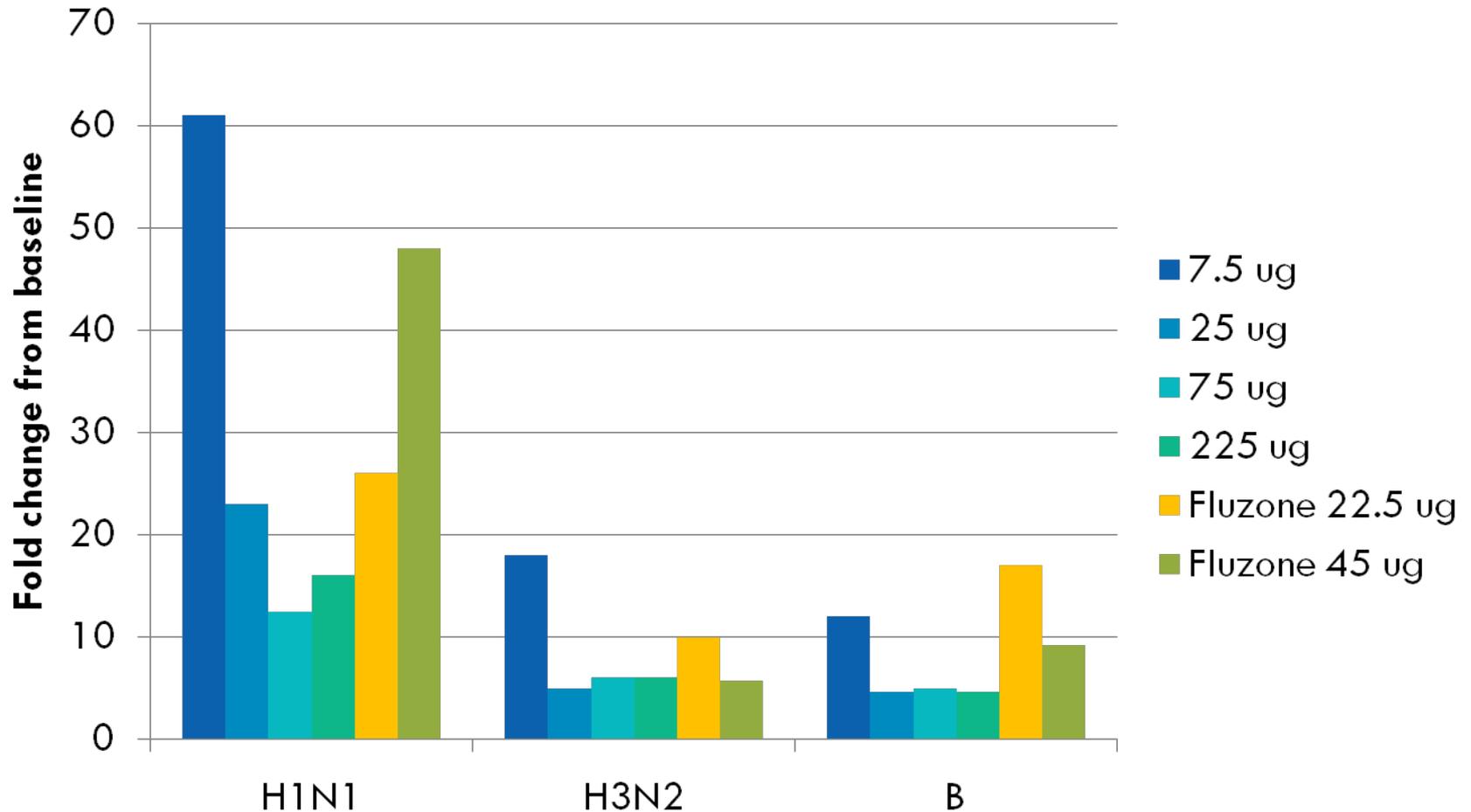
- Double-blind study, healthy adults 18–49 years (N=128)
- Single IM injection of Fluzone[®] +/- JVRS-100

Group	N	JVRS-100	Fluzone [®]
1	20	7.5 µg	22.5 µg
2	20	25 µg	22.5 µg
3	20	75 µg	22.5 µg
4	20	225 µg	22.5 µg
5	24	-	22.5 µg
6	24	-	45 µg

- Primary Endpoints: Safety and tolerability (dose)
- Secondary Endpoints:
 - Antibody responses (HAI and Neutralization assays)
 - T-cell responses by ICS

Adverse Event by Cohort	JVRS-100 + Fluzone No. subjects (%)				Fluzone No. subjects (%)	
	7.5 µg N=20	25 µg N=19	75 µg N=20	225 µg N=20	22.5 µg N=25	45 µg N=24
Abdominal pain	0	0	0	2 (10)	2 (8)	1 (4)
Diarrhea	1 (5)	0	1 (5)	1 (5)	1 (4)	3 (13)
Nausea	1 (5)	0	1 (5)	4 (20)	1 (4)	1 (4)
Chills	2 (10)	1 (5)	2 (10)	4 (20)	2 (8)	0
Fatigue	5 (25)	1 (5)	8 (40)	13 (65)	5 (20)	5 (21)
Feeling hot	5 (25)	2 (11)	1 (5)	10 (50)	2 (8)	0
Injection site erythema	1 (5)	0	2 (10)	5 (25)	2 (8)	1 (4)
Injection site pain	10 (50)	13 (68)	18 (90)	18 (90)	9 (36)	14 (58)
Injection site pruritus	0	1 (5)	0	2 (10)	1 (4)	0
Injection site swelling	1 (5)	1 (5)	3 (15)	5 (25)	1 (4)	0
Malaise	4 (20)	2 (11)	1 (5)	10 (50)	2 (8)	4 (17)
Upper respiratory infection	0	1 (5)	0	0	4 (16)	1 (4)
Hemoglobin decrease	0	1 (5)	0	2 (10)	1 (4)	2 (8)
WBC increase	2 (10)	0	0	0	1 (4)	0
Arthralgia	1 (5)	1 (5)	2 (10)	4 (20)	4 (16)	1 (4)
Myalgia	5 (25)	1 (5)	4 (20)	7 (35)	5 (20)	3 (13)
Dizziness	0	2 (11)	0	0	0	0
Headache	7 (35)	4 (21)	5 (25)	9 (45)	3 (12)	6 (25)
Somnolence	3 (15)	1 (5)	3 (15)	8 (40)	3 (12)	3 (13)

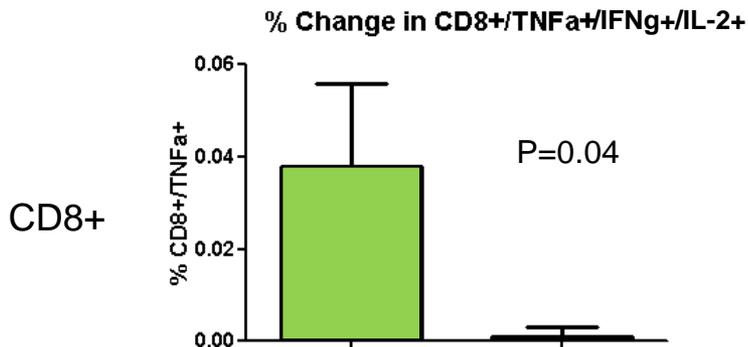
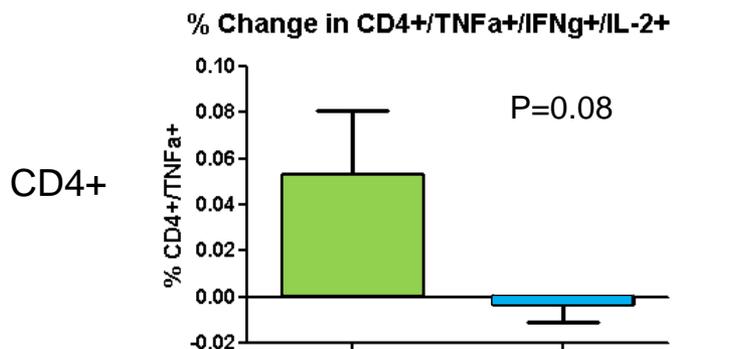
Phase 1 Dose Response, Neutralizing Antibodies – JVRS-100 with 22.5 ug HA



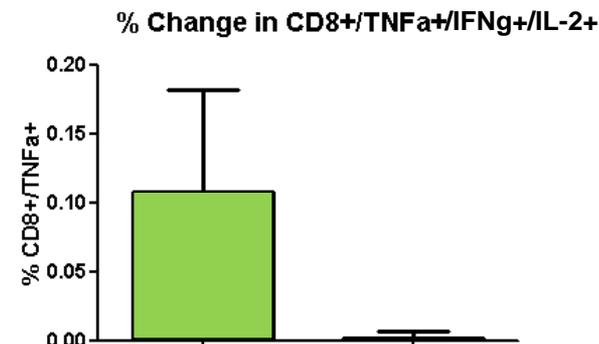
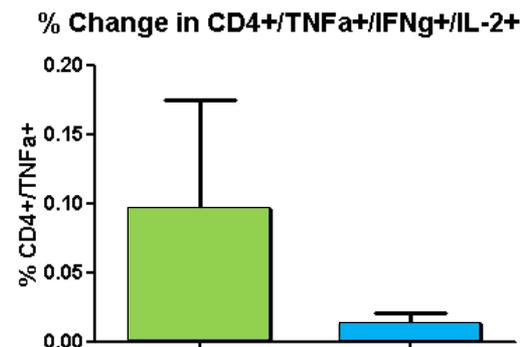
Poly-Functional T-Cell Responses

Ph 1 Data: Intracellular Cytokine Staining 7.5 μ g dose

Flu A (H3N2)



Flu B



 = 7.5 μ g JVRS-100 + 22.5 μ g TIV (N=20)

 = 22.5 μ g TIV (N=23)

Juvaris Phase 2 Clinical Trial (H-100-002)

Adjuvanted trivalent inactivated influenza vaccine in the elderly

- Phase 2 study initiated November 2009
- Interim analysis (HAI response data) March 2010
 - Reduced antibody response compared to TIV without adjuvant
 - If JVRS-100 immunosuppressive, results could have implications for other indications, including immunotherapy of leukemia.
- Voluntarily halted enrollment in Ph 1 AML April 2010
 - Subjects enrolled to date (6) in the Phase 1 Leukemia study were investigated for markers of immune activation.
 - Additionally, sera from Leukemia patients was tested for cytokine response during the acute (24 hr) post-infusion period.
- A subset of subjects from the Phase 2 influenza vaccine clinical trial was analyzed for T-cell responses.

Juvaris Phase 2 Clinical Trial (H-100-002)

Adjuvanted trivalent inactivated influenza vaccine in the elderly

- Phase 2 Study is on-going and remains blinded
 - Subjects now completing 9-month follow-up visits (study conclusion)
 - Final database lock ~Oct 2010
 - Preliminary safety data unblinded (thru 28 days post-vaccination) + SAE information (thru 4 months post-vaccination).
 - No treatment-related SAEs or other safety signals of concern, and vaccination was well tolerated

Phase 2 Study Objectives & Design

- ❑ Assess safety, tolerability of Fluzone administered with JVRS-100 in persons aged ≥ 65 years.
- ❑ Determine optimal dose of JVRS-100 adjuvant
- ❑ Determine the adjuvant effect of JVRS-100 as measured by HAI and neutralizing antibodies and T-cell responses (using various assays).

Group	N	Treatment
A	118	45 μ g Fluzone with 3.75 μ g of JVRS-100
B	118	45 μ g Fluzone with 7.5 μ g of JVRS-100
C	118	45 μ g Fluzone with 25 μ g of JVRS-100
D	118	45 μ g Fluzone only

- 85% power (2-sided $\alpha=0.05$) to detect a ≥ 1.5 -fold difference in HAI titer between 2 dose groups
- 80% power to detect a difference in polyfunctional T-cells between optimal JVRS-100 dose group and Fluzone



Adverse events

- The adjuvant was well-tolerated
- Increased injection site reactions in JVRS-100 treatment groups vs. Fluzone, mostly mild, not dose related (except injection site pain)
- Slight increase in fatigue in JVRS-100 groups vs. Fluzone, but not other systemic Aes
- Total of 43 SAEs through month 4

Grade	Number of events	Number related
4	4	0
3	22	0
1-2	17	0



Phase 2

HAI Titer 28 Days Post-Vaccination

Antigen	Parameter	JVRS-100 and Fluzone			Fluzone only
		3.75 ug	7.5 ug	25 ug	
H1N1	GMT Day 0	28.4	19.8	23.9	25.2
H3N2		51.3	39.1	33.0	36.6
B		18.1	13.6	13.4	15.7
H1N1	GMT Day 28	71.1	59.3*	52.6*	92.4
H3N2		299.6	229.9	153.3*	320.0
B		43.0	36.7	29.2*	49.5

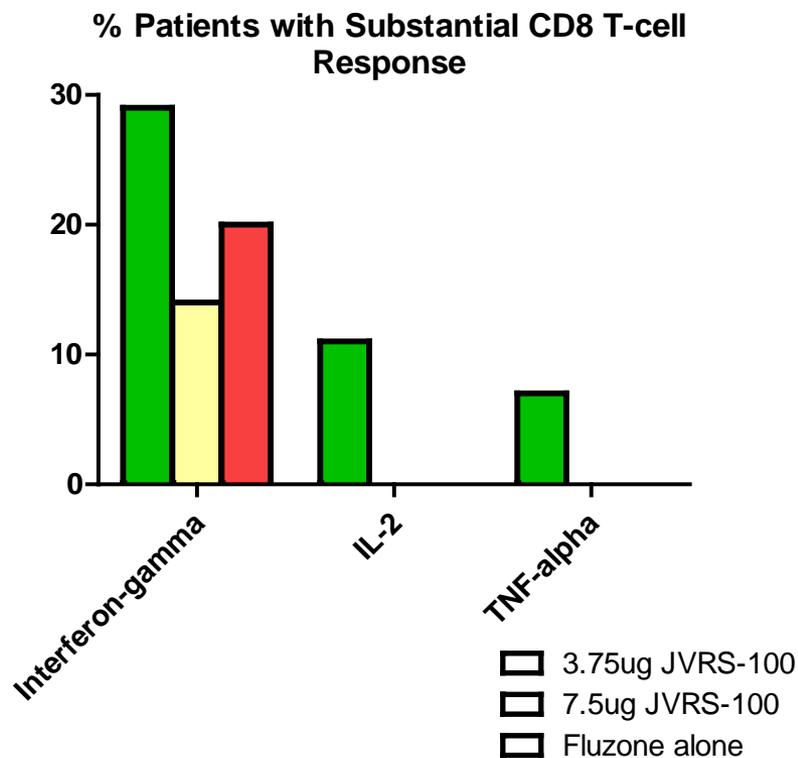
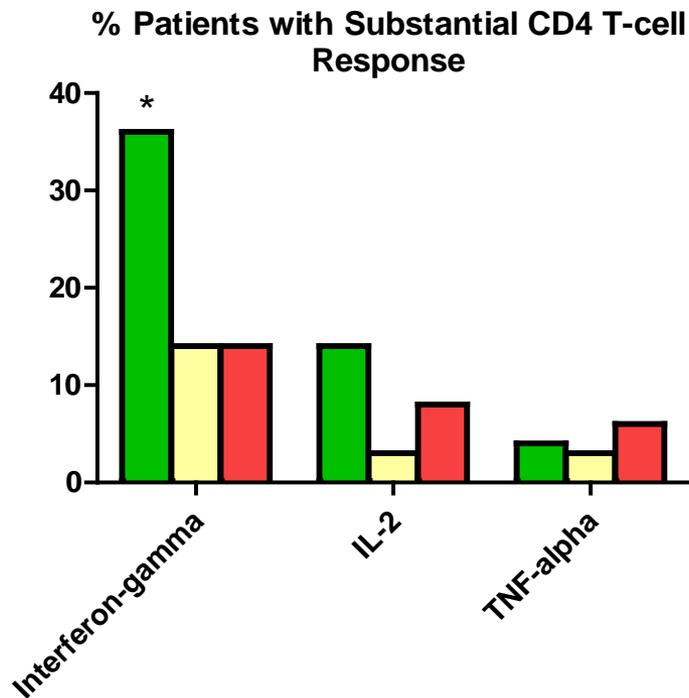
* p<0.05 pairwise comparison JVRS group vs. Fluzone, Dunnett's test

Seroprotection Rate (% with HAI >40) 28 Days Post-Vaccination

Antigen	Parameter	JVRS-100 and Fluzone			Fluzone only
		3.75 ug	7.5 ug	25 ug	
H1N1	Sero-protected (%) Day 28	79.7	78.4	73.1	82.2
H3N2		90.7	95.7	87.4	94.1
B		57.6	52.6	45.4*	70.3

* 95% CI non-overlapping with Fluzone only group

Substantial Response Rate of CD4 and CD8 in Lowest Adjuvant Group in Phase 2 TIV Study



* Statistically significant increase in responders ($p=0.0446$ vs. Fluzone[®] alone), when analyzed by a two-tailed Fisher's exact test.

Summary and Interpretation-1

- JVRS-100 appeared to suppress the HAI antibody response in a dose-dependent manner
 - Statistically lower immune response at highest JVRS-100 dose (25 μ g)
 - Trend for immune suppression at 3.75 and 7.5 μ g doses
 - These observations held across multiple endpoints (GMT, fold-change, seroprotection, seroconversion)
- Obvious discrepancy between clinical and preclinical data, including NHP models
 - Preclinical models show consistent adjuvant effects in the setting of primary immunization
 - One study in elderly macaques with prior flu exposure also showed adjuvant activity

Summary and Interpretation-2

- Hypothesis: JVRS-100 immune suppression is associated with pre-existing immunity
 - JVRS-100 activated feedback loop
 - preventing over stimulation in setting of memory B (T) cell pool
 - Probable unique immunosuppressive cytokine profile
 - studies underway to define
 - More pronounced in elderly vs. young adults
 - more prior exposures to flu
 - Some evidence for similar phenomena with other adjuvants (QS21, CpG)
 - Funded R01 will test our hypothesis

Acute Myelogenous Leukemia

JVRS-100 Clinical Development

- JVRS-100 in AML
 - Anti-tumor effects driven by T_H1 cytokines and NK cell activation
 - Survival benefit demonstrated in multiple pre-clinical models
- Clinical Development: Phase 1/2 Protocol Design
 - Study Design –
 - Relapsed AML, ALL and MDS patients (N = 23)
 - JVRS-100 IV q7-10 days x 3 infusions per cycle for up to 6 cycles
 - Stage 1: 3-6 subjects at each dose level to determine RP2D
 - Stage 2: Expanded cohort to assess safety and efficacy of RP2D
 - Objectives
 - Safety, MTD and RP2D
 - Efficacy: Objective response, durability of response and survival
 - Status
 - 3 patients dosed at 0.1ug/kg and 0.5ug/kg, respectively
 - No adverse events related to study material
 - Upregulation of cytokines seen on protein microarray

Acute Myelogenous Leukemia - JVRS-100 Study

Dose-Escalation Schedule for Stage 1 (Accelerated Titration)	
Dose Levels	Dose and schedule of treatments/cycle
Level 1	0.1 µg/Kg D1, 8, 15
Level 2	0.5 µg/Kg D1, 8, 15
Level 3	1.0 µg/Kg D1,8,15
Level 4	2.0 µg/Kg D1,15
Level 5	2.0 µg/Kg D1, 8, 15
Level 6	4.0 ug/Kg D1, 15

Change to Stage 2 with starting dose of 4.0 ug/Kg D1, 8, 15 if no toxicity by Level 5

Dose-Escalation Schedule for Stage 2 (Modified Fibonacci)	
Dose level	Dose
Level 1	To start when accrual to stage 1 is terminated
Additional levels	35% increments until DLT is reached in $\geq 2/6$ patients. Maximum dose that will be tested is 5.4 µg/kg
RP2D	Expand cohort to a total of 12 patients

Clinical Experience in AML

- 6 Patients enrolled with relapsed and refractory AML

Total Enrollment	6
Patients on Active Treatment	0
Patients Completed Treatment	0
Off Treatment Due to Disease Progression	6
Patients on Follow-Up	0
Termination associated with an adverse experience	0

Adverse Events: Frequent and Serious

- Events considered possibly related consisted of nineteen grade 1&2 events: Gastrointestinal (8); Constitutional (4); Skin & subcutaneous skin (3); Musculoskeletal (2); Cardiac (1); and Eye (1).
- There were twenty grade 3&4 events (primarily Blood and lymphatic system disorders) that were considered unrelated to the study.
- There were two reported SAE's, both due to infection and considered unrelated to the study drug.

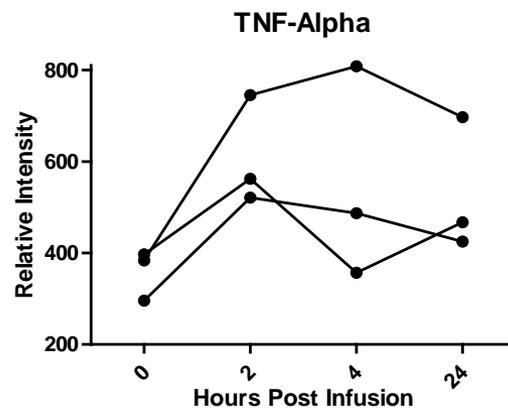
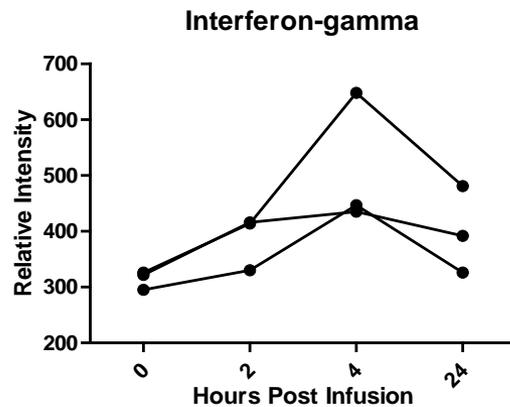
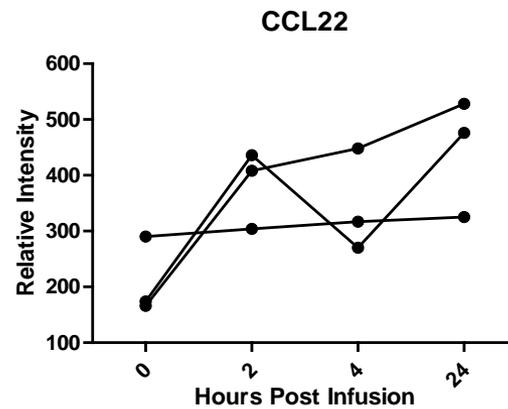
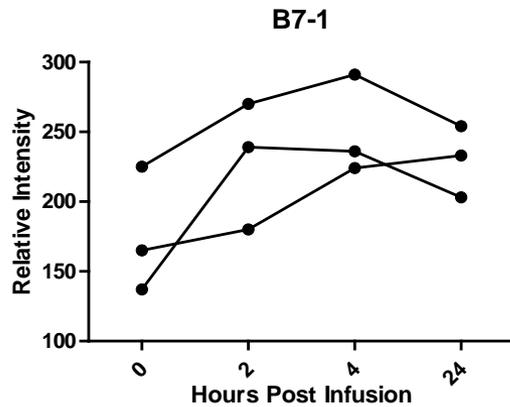


Correlative Studies: Leukemia Trial

- Detailed Flow cytometry of PBMNC before and after each infusion. No changes in T or B cell numbers or activation profile.
- Detailed cytokine array analysis for patients in cohort 2. Most cytokines studied showed no consistent changes.



Microarray analysis shows immunostimulatory T_H1 response following IV admin of JVRS-100



- B7-1 is a molecule found on activated B-cells and monocytes which provides a co-stimulatory signal necessary for T-cell activation and survival;
- CCL22 is a chemotactic factor for monocytes, dendritic cells and natural killer cells;
- interferon-gamma (IFN- γ) is a cytokine that is critical for innate and adaptive immunity against viral and intracellular bacterial infections and for tumor control; and
- TNF- α is able to inhibit tumorigenesis and viral replication.

FDA Feedback from Medical Reviewer

- IND 13766
- Medical Reviewer: Bindu George, MD
- Feedback Received: 14 SEP 2010
 - Immune activation observed in the study validates expected mechanism of action
 - Efficacy-related data from the flu vaccine study had no clear implications for safety of patients enrolled in the Leukemia study.
 - Therefore, saw no reason to request a clinical hold on Leukemia study, and feel that the study may resume accrual.





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