

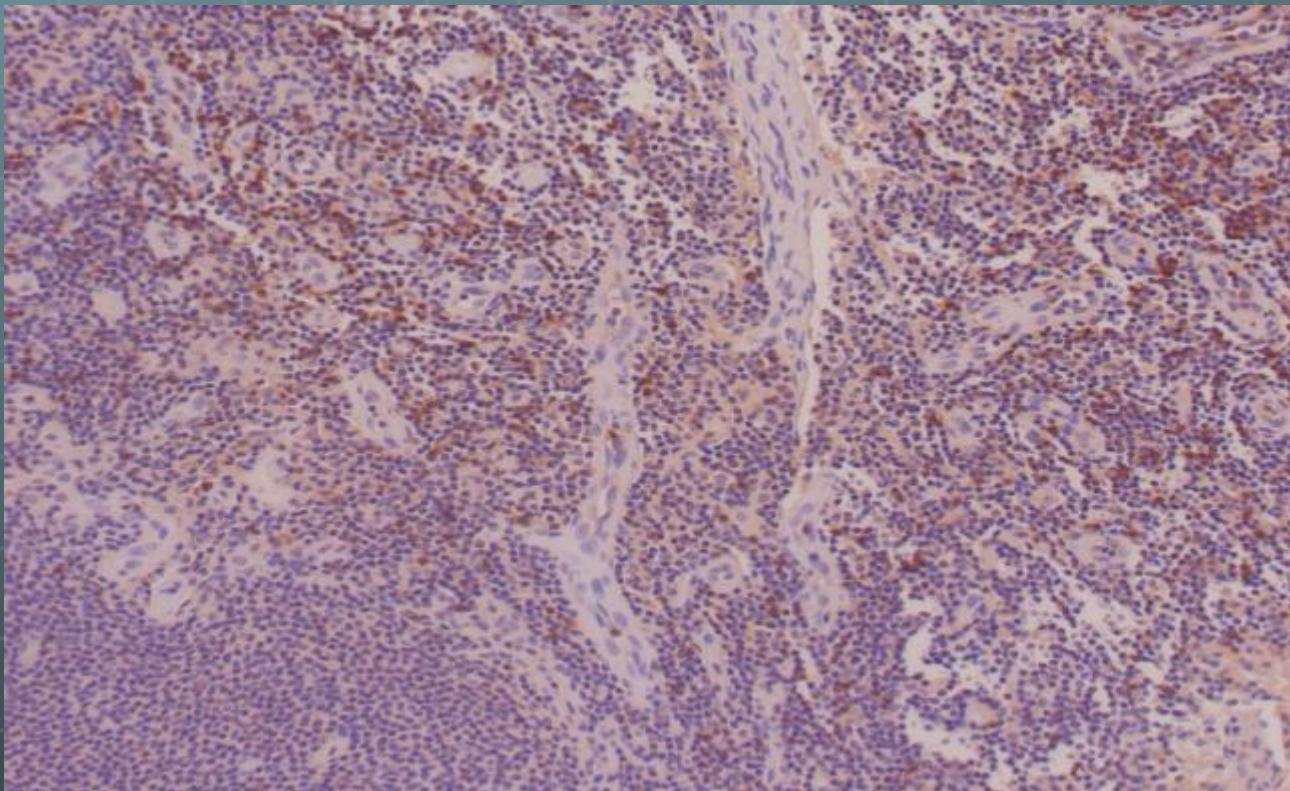
Rocket science & Immuno control dynamics

Harold P. Frisch
NASA/GSFC/Emeritus
Mayo Clinic Consultant
May 1, 2012

Collaboration Team

- Mayo Clinic - Cancer Immunology and Immunotherapy
 - Svetomir Markovic, M.D., Ph.D.
 - Alexey Leontovich, Ph.D.
 - Wendy Nevala
- Texas A&M University – Aerospace engineering
 - James Turner, Ph.D.
- Rebellion Photonics – Hyperspectral imaging technology
 - Robert Kester, CTO
- NASA/GSFC – Systems engineering
 - Harold P. Frisch, Emeritus

It all started with one Melanoma slide



Multi-cellular interaction dynamics
Explain telltale signatures

Wanted - New Eyes



Thus, the task is not so much to see what no one yet has seen, but to think what nobody yet has thought about that which everybody sees.

Schopenhauer

With new views



In solving a problem of this sort, the grand thing is to be able to reason backwards. That is a very useful accomplishment, and a very easy one, but people do not practice it much.

Sherlock Holmes,
in Sir Arthur Conan Doyle's
A Study in Scarlet

Outline

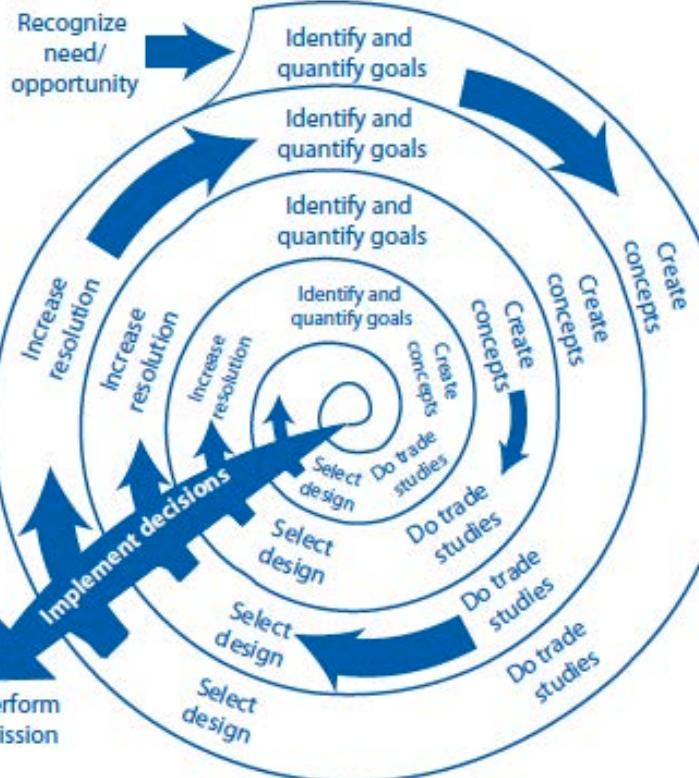


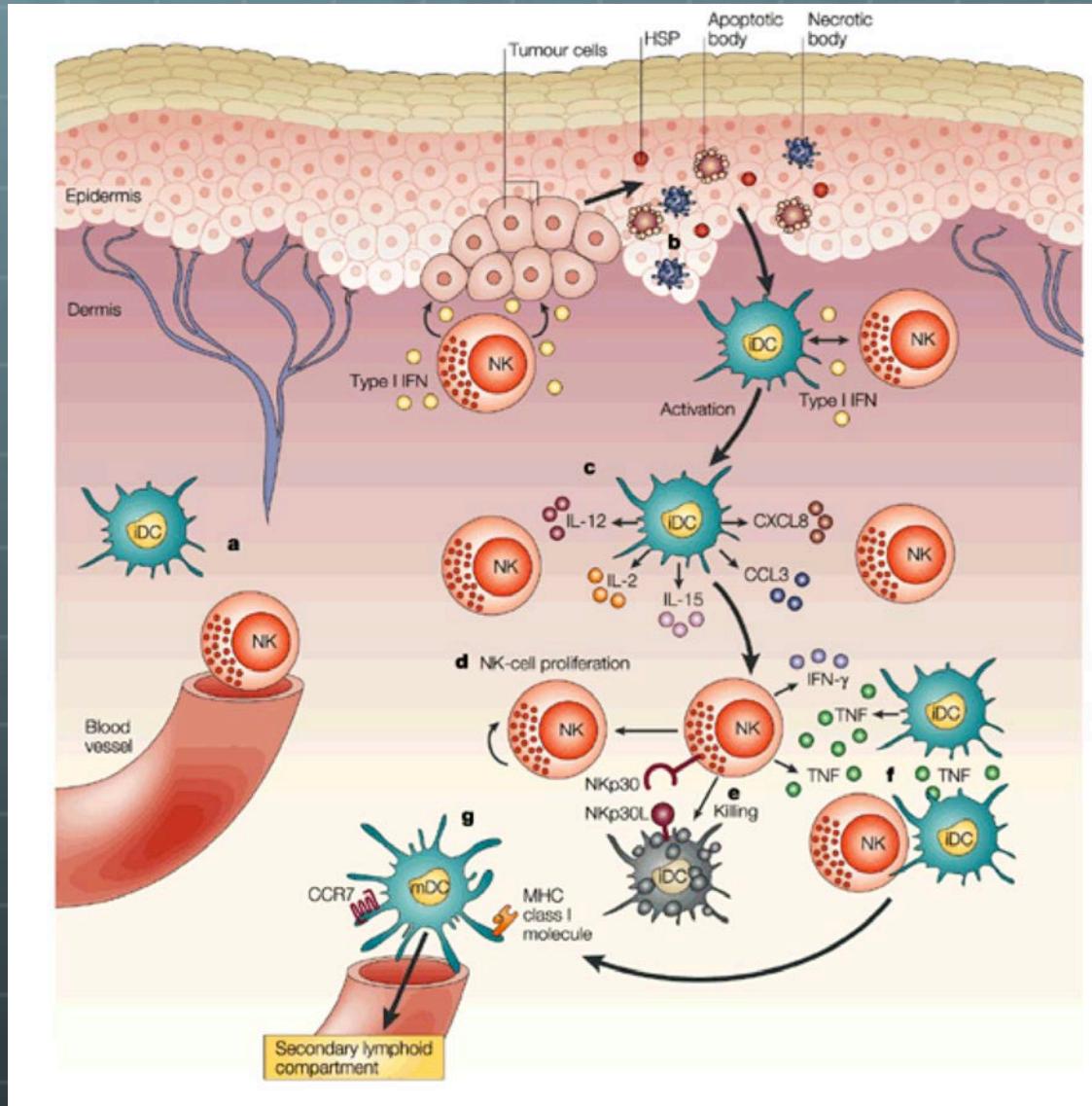
Figure 4.4-2 The doctrine of successive refinement

56 • NASA Systems Engineering Handbook

Successively refining rocket science views

- Concepts all apply
- None apply as expected
- Patient data - Reality
- Math analysis - Views
- Today – An overview of concepts applied on what, why & how

Immuno control dynamics



Immuno control dynamics observable data

- Patient - blood sampling
 - Remote from the Tumor Microenvironment
- Petri-dish – Model of Tumor Microenvironment in a Immuno cell/cytokine culture
- Measurements yield population size (counts)
 - Many bio-actions cause population size change
- Data very sparse (time-cost reality limited)
 - Petri-dish: One sample per day
 - Patient: One sample per month
 - One sample = \$150 supplies + 1 lab skilled worker day
- Lots of bio-dynamics going on between sampling

Patient enrolled in trial and pretreatment blood drawn.

Patient receives treatment about every 4 weeks with a blood draw prior to each treatment.

Patient has tumor progression, goes off study and has final blood draw.

20 to 50ml of blood comes to the lab for processing.

Sample is spun to separate plasma from white blood cells

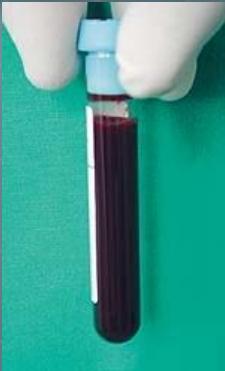
Plasma collected, frozen and stored in 1ml aliquots.

White blood cells isolated from blood, frozen and stored in 1ml aliquots.

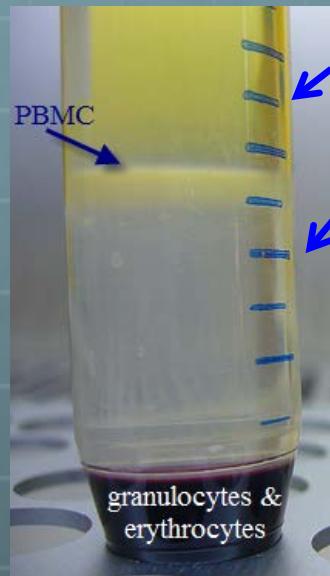
Blood concentrations of 42 cytokines are measured in pg/ml.

Blood frequencies of white blood cell types are measured in percentage.

20 to 50ml of blood comes to the lab for processing.



Layer blood over ficoll (sugar solution) and spin in centrifuge

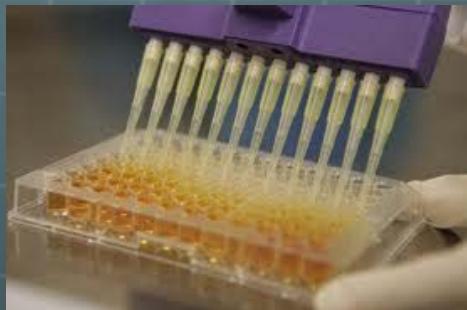


Plasma and PBMC stored frozen in aliquots



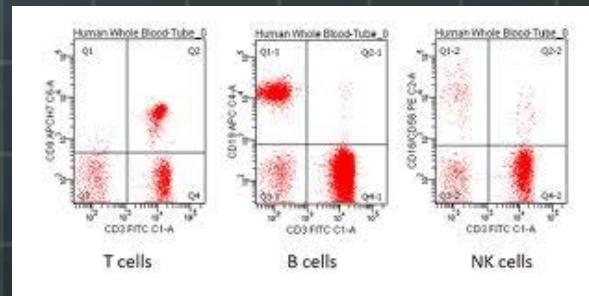
Plasma

White Blood Cells (PBMC)



Well	Sample Name	Group Name	Expect...	MF1	MF1 Average	Count	Concentration	Conc. Average
Read Name: GM-CSF								
A2	Background	Bkg001		39.0	0.00	194	1.4	1.52
A1	Background			41.0		189	1.6	
B2	Std 1		20000.00	10054.5	10235.25	152	18198.0	20137.25
B1	Std 1		4000.00	10516.0	6185.50	208	22076.0	
C2	Std 2		6299.0	6152.0	246	4063.0	3940.68	
C1	Std 2		4000.0	2990.5	225	3818.0		
D2	Std 3		800.00	3104.0	3007.25	252	797.5	826.56
D1	Std 3			1094.0		213	655.0	
E2	Std 4		160.00	1040.0	1027.00	223	156.0	153.09
E1	Std 4			300.0		181	147.0	
F2	Std 5		32.00	292.0	256.00	217	28.7	28.31
F1	Std 5			104.0	66.25	165	27.8	
G2	Std 6		6.40	108.5	190	259	7.4	
G1	Std 6			55.0	202	7.6	7.67	
H2	Std 7		1.28	56.0	15.50	183	2.7	2.91
H1	Std 7							

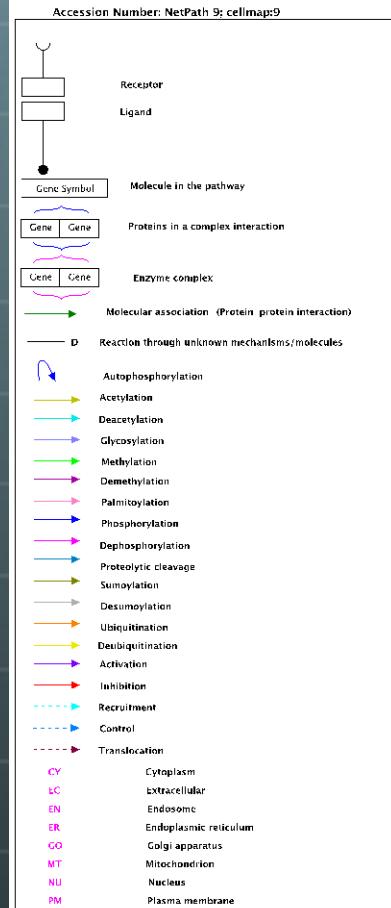
Cytokine concentrations in blood plasma



Percentages of white cell subsets in blood

Cellular printed circuitry

Title: TNF-alpha/NF- κ B Signaling Pathway
Email: cellmap-info@cell-map.org
Availability: Freely available under Creative Commons License
Last modified: 07-JUN-16
Organism: Homo sapiens
Data Source: GenMAPP 2.0



Analysis foundation



Aerospace

- Equations known
- Rate of change of momentum=Load
- Given equations, constants & Loads find output
- Compute output & compare to desired output
- Many feedback control analysis tools
 - Link to Immuno-biology
 - Modify to support Immuno control
 - Modify to support emergent behaviour



Immuno-biology

- Equations unknown
- Rate of change of Effect=Cause
- Many observational relationships
- Given relationships + output find Cause
- Assume approximate form for Causal relationships
- Derive associated unknown constants
- Compute output & compare with measured output
- Link to Feedback control tools

Control dynamics problem foundation

- Aerospace
 - Newton's equations
 - Linear oscillatory
 - Linear signal analysis
 - Source - springs & dampers
 - Linear springs, dampers
 - Conservation of xxx
 - Feedback sensors
 - Relative position (-) control
 - Minimal redundancy
 - Minimally adaptable
 - Minimal concurrent interaction
 - Fragile stability
 - Deterministic behaviour
- Immuno-biology
 - Predator-Prey equations
 - Non-linear oscillatory
 - Nonlinear signal analysis
 - Sources-Triggers-Modulators
 - Tri-linear springs
 - Homeostasis
 - Cytokine message carrier
 - Population size (x) control
 - Massive redundancy
 - Massively adaptable
 - Massive concurrent interaction
 - Robust stability
 - Emergent (natural) behaviour

Newtonian equations linearized

$$\frac{d\text{Mass} * \text{Velocity}}{dt} = \text{Spring} * \text{Position} + \text{Damper} * \text{Velocity}$$
$$\frac{d\text{Position}}{dt} = \text{Velocity}$$

- ➊ Rate of change of momentum = Loads applied
- ➋ Linearization yields linear mass spring damper equation
- ➌ Position links to velocity by differential relationship
- ➍ Response – linear harmonic motion

Lotka-Volterra Predator Prey Equations

$$\frac{dFox}{dt} = aFox + bFox * Rabbit$$

$$\frac{dRabbit}{dt} = cRabbit + dRabbit * Fox$$

- Foxes reproduce and need survival food
- Rabbits reproduce and need reproduction control
- Interaction dynamics essence lost in linearization
- Used extensively to model bio-system dynamics
- Response non-linear oscillatory with Hopf bifurcation

Computational methods

- **Finite element theory**
 - Force-displacement ODEs
 - Linear spring
 - Visco-elastic
force(constant*displacement + constant*velocity)
 - Model via network of interconnected linear springs
 - CAD model
 - Visualization
 - Input mass, spring, damper constants
 - Perturb system and predict linear system harmonic response

ODEs-Ordinary Differential Equations

* New – Specifies all **potential** Cause-effect relationships

- **Finite relationship theory***
 - Cause-Effect ODEs
 - Population growth
cause(constant*source*trigger*modulator)
populations
 - Model via network of interconnected Uni, Bi & Tri-linear springs
 - Knowledge Model
 - Visualization
 - Input observed response
 - Predict network constants
 - Compute Causal impacts that yield non-linear oscillatory response of observable Effects

Knowledge Model

- **Observable Effects** impacted by bio-action
- Every bio-action has a **Source (Observable Effect)**
- Source bio-actions are **Triggered (Observable Effect)**
- Source bio-actions are **Modulated (Observable Effect)**
- Bio-actions have many characterization:
 - Secretion, proliferation, recruitment, activation, etc.
 - Modeled as Constant, Uni, Bi or Tri-linear expressions
 - Such expressions are approximations to bio-reality
- **Knowledge model** collects all such relationships

Causal impact approximation

Kolmogorov-Gabor polynomial

- Kolmogorov-Gabor polynomials have been used widely to evolve general non-linear models
 - Heuristic self-organization studies
 - Neural network learning
- All {x's} are **known** measured observables; e.g. CD3,IL-2,...
- All {u's} are **to-be-determined** unknowns

$$Y(x_1, x_2, \dots, x_n) = u_0 + \sum_i x_i u_i + \sum_i \sum_j x_i x_j u_{i,j} + \sum_i \sum_j \sum_k x_i x_j x_k u_{i,j,k}$$

Living in the Fast-Lane of the Curse of Dimensionality for Bio Modeling

The Problem:

General Model Formulations Lead to an **Exponential Explosion** in the number of unknowns to be Defined (See Below—NOT GOOD!)

$$Y(x_1, x_2, \dots, x_n) = u_0 + \sum_i x_i u_i + \sum_{i, j} x_i x_j u_{i,j} + \sum_{i, j, k} x_i x_j x_k u_{i,j,k}$$

COMMENT: Though Theoretically Valid, If One Insists on Mathematical Purity, You Pay with unrecoverable Computational Difficulties, arising from a Lack of Data for Algorithm Observability.

How do we shrink the Problem down to manageable size, while retaining Predictive Power????

Abandon Algorithm Purity by Invoking Interaction Constraints Defined by Previously Identified **Knowledge Model**: Goal is to Eliminate as many Unknowns as Possible

Develop a **Predator - Prey** Based Reverse Engineering Bio-Dynamics Inverse Problem Alg.: Recover Differential Equations, where Coefficients are Derived from Clinical Data

Original Problem Size



Problem Size after Knowledge Model Invoked



Problem Size after Predator - Prey



Reverse engineering

From observations to causes

- E – Effect population (count) is union of all (S) sources, (T) triggers and (M) modulators

$$E = S \cup T \cup M$$

- Population changing bio-action Causal impact is sum of all potential components, data defines respective strength of potential contributors

- Insight comes from connectivity between Causal Impacts and predicted Effect response

- Dynamics relationship – rate of change of Effect population equal to the sum of all Causal impacts

$$\left\{ \frac{dE}{dt} \right\} = [S * T * U] \{u\}$$

- With observed Effect data & Knowledge model use Singular Value decomposition to compute all values of {u}

- With all values of {u} compute all Causal impacts

Proof of concept

- ➊ Math sanity checks
 - ➊ Started small - Knowledge model just contained the obvious
 - ➋ Used only basic Knowledge model framework
 - ➌ Used Math to “see” into Cause & Effect dynamics

- ➋ Bio sanity checks
 - ➊ Communicate derived response characterization math views to Immuno-experts
 - ➋ Explain the unexpected
 - ➊ Petri dish test of first anomaly confirmed to be bio-real

- ➌ Done (to-date) – Many random explorations
 - ➊ Lots of bio-variability overlays patient agnostic response patterns
 - ➋ Need to expose patient agnostic response patterns

- ➍ Extending software to accommodate ALL potential connectivity
 - ➊ Let the data find the ignorable
 - ➋ Let the data find the analysis path to Clinical relevance

Examples of Raw data

Raw data PD-noVEGF CD11c.14



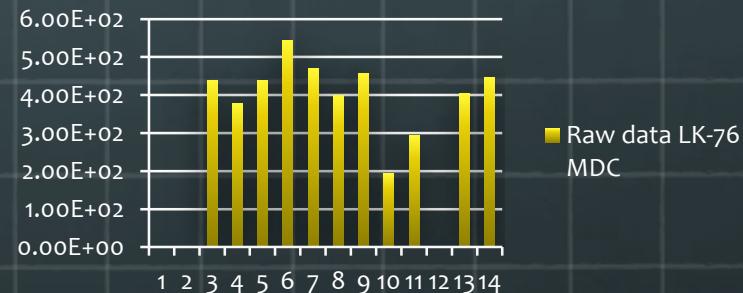
Raw data LK-76 CD11c.14



Raw data PD-noVEGF IL-10



Raw data LK-76 MDC

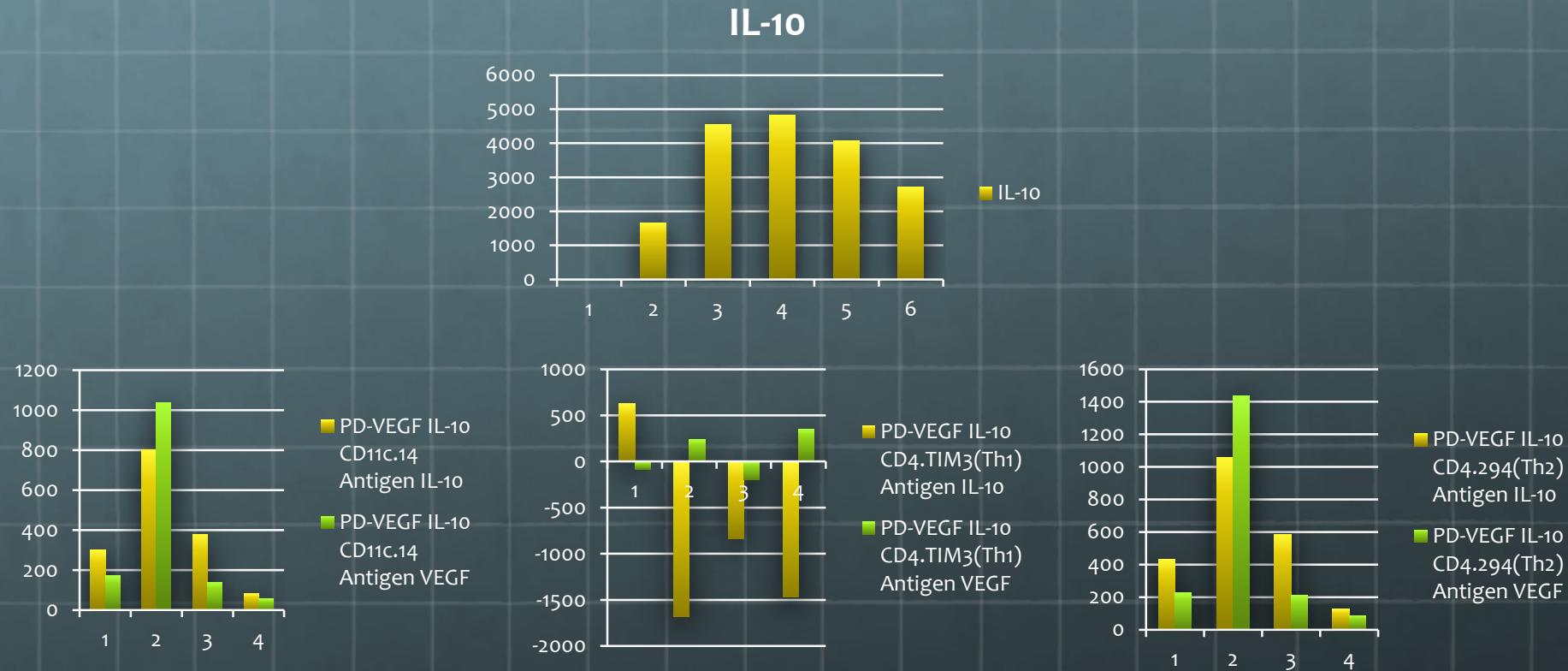


Influence (Causal impact) arrays

Petri dish vs. Patient

PD-VEGF		M	O	D	U	L	A	T	O	R	S	sCD40L	sIL-2Ra	TNF α	TNF β	
		GRO	IL-1b	IL-2	IL-8	IL-13	IP-10	MCP-1	MIP-1a	MIP-1b	RANTES					
CD11c.14	12.50	84.26	8.41	2.52	3.23	4.21	11.74	2.84	5.70	11.16	12.82	21.79	7.08	34.80	27.98	
CD11c.14	1.00	1.96	0.35	0.47	0.80	1.65	4.59	0.06	1.66	4.71	5.01	7.05	3.86	2.17	0.21	
GM-CSF	0.60	3.38	0.43	0.27	0.46	0.95	2.66	0.07	0.98	2.73	2.90	4.17	2.24	1.27	0.27	
GRO	0.41	7.60	0.88	0.19	0.32	0.66	1.84	0.15	0.68	1.89	2.01	2.88	1.55	0.88	0.54	
E	IL-1b	1.46	24.42	1.31	0.29	0.41	0.46	1.28	0.22	1.79	1.31	1.40	7.64	1.18	0.21	
F	IL-2	1.17	21.15	0.64	0.21	0.41	0.26	0.74	0.08	1.41	0.02	0.81	5.93	0.70	1.55	
F	IL-8	1.17	21.15	0.64	0.21	0.41	0.26	0.74	0.08	1.41	0.02	0.81	5.93	0.70	1.55	
E	IL-13	0.73	2.83	0.49	0.21	0.34	0.71	1.99	0.07	0.76	2.04	2.17	3.62	1.69	1.00	
C	IP-10	0.90	2.11	0.29	0.42	0.73	1.49	4.16	0.02	1.49	4.26	4.54	6.33	3.49	1.95	
T	MCP-1	0.92	17.49	0.51	0.15	0.37	0.36	1.00	0.08	1.08	1.02	1.09	4.53	0.83	1.18	
S	MIP-1a	1.17	21.15	0.64	0.21	0.41	0.26	0.74	0.08	1.41	0.02	0.81	5.93	0.70	1.55	
	MIP-1b	0.64	3.22	0.40	0.29	0.49	1.02	2.85	0.06	1.05	2.92	3.11	4.48	2.41	1.37	
	RANTES	0.67	13.85	0.37	0.16	0.33	0.57	1.60	0.05	0.76	1.64	1.74	3.13	1.34	0.81	
	sCD40L	0.80	4.26	1.80	0.38	0.64	1.32	3.69	0.31	1.32	3.78	4.03	5.61	3.10	1.73	
	sIL-2Ra	1.50	4.64	1.02	0.30	0.24	0.61	1.71	0.14	1.57	1.87	1.87	7.47	1.94	2.05	
	TNF α	1.17	21.15	0.64	0.21	0.41	0.26	0.74	0.08	1.41	0.02	0.81	5.93	0.70	1.55	
	TNF β	1.37	5.24	1.09	0.28	0.29	0.62	1.75	0.18	1.43	1.80	1.91	6.80	1.77	1.87	
LK-28		M	O	D	U	L	A	T	O	R	S	sCD40L	sIL-2Ra	TNF α	TNF β	
CD11c.14	IL-10	VEGF	GM-CSF	GRO	IL-1b	IL-2	IL-8	IL-13	IP-10	MCP-1	MIP-1a	MIP-1b	RANTES			
CD11c.14	0.15	0.41	0.1	15.88	0.08	0	4.57	3.79	37.39	3.97	0.02	0.26	0	45.45	0	
GM-CSF	0.01	0.04	0.02	0.2	0.01	0	0.29	0.02	1.97	2.49	0.31	0.98	0	16.7	0	
GRO	0	0.01	0	0.01	0	0	0.04	0	0.14	0.16	0.01	0.03	0	7.89	0	
IL-10	0	0.02	0.01	0.09	0.01	0	0.14	0.01	0.93	1.18	0.15	0.47	0	7.92	0	
E	IL-13	0	0.01	0	0.01	0	0	0.02	0	0.14	0.17	0.02	0.07	0	7.62	0
F	IL-1b	0.01	0.04	0.03	0.2	0.01	0	0.3	0.02	2.04	2.59	0.32	1.02	0	17.35	0
F	IL-2	0	0	0	0.01	0	0	0.04	0	0.09	0.12	0.02	0.05	0	3.69	0
E	IL-8	0.01	0.04	0.03	0.2	0.01	0	0.3	0.02	2.04	2.58	0.32	1.02	0	17.32	0
C	IP-10	0.01	0.04	0.02	0.18	0.01	0	0.27	0.02	1.85	2.35	0.29	0.93	0	15.72	0
T	MCP-1	0.01	0.04	0.03	0.2	0.01	0	0.3	0.02	2.01	2.55	0.32	1.01	0	17.1	0
S	MIP-1a	0.01	0.04	0.03	0.21	0.01	0	0.32	0.02	2.15	2.73	0.34	1.08	0	18.27	0
	MIP-1b	0.01	0.04	0.03	0.21	0.01	0	0.32	0.02	2.13	2.7	0.34	1.07	0	18.13	0
	RANTES	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	sCD40L	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	sIL-2Ra	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	TNF α	0.01	0.04	0.02	0.2	0.01	0	0.29	0.02	1.98	2.51	0.31	0.99	0	16.84	0
	TNF β	0	0	0	0.01	0	0	0.01	0	0.07	0.08	0.01	0.02	0	4.1	0

Causal Impact analysis detail (example)



Positive values imply cytokine secretion

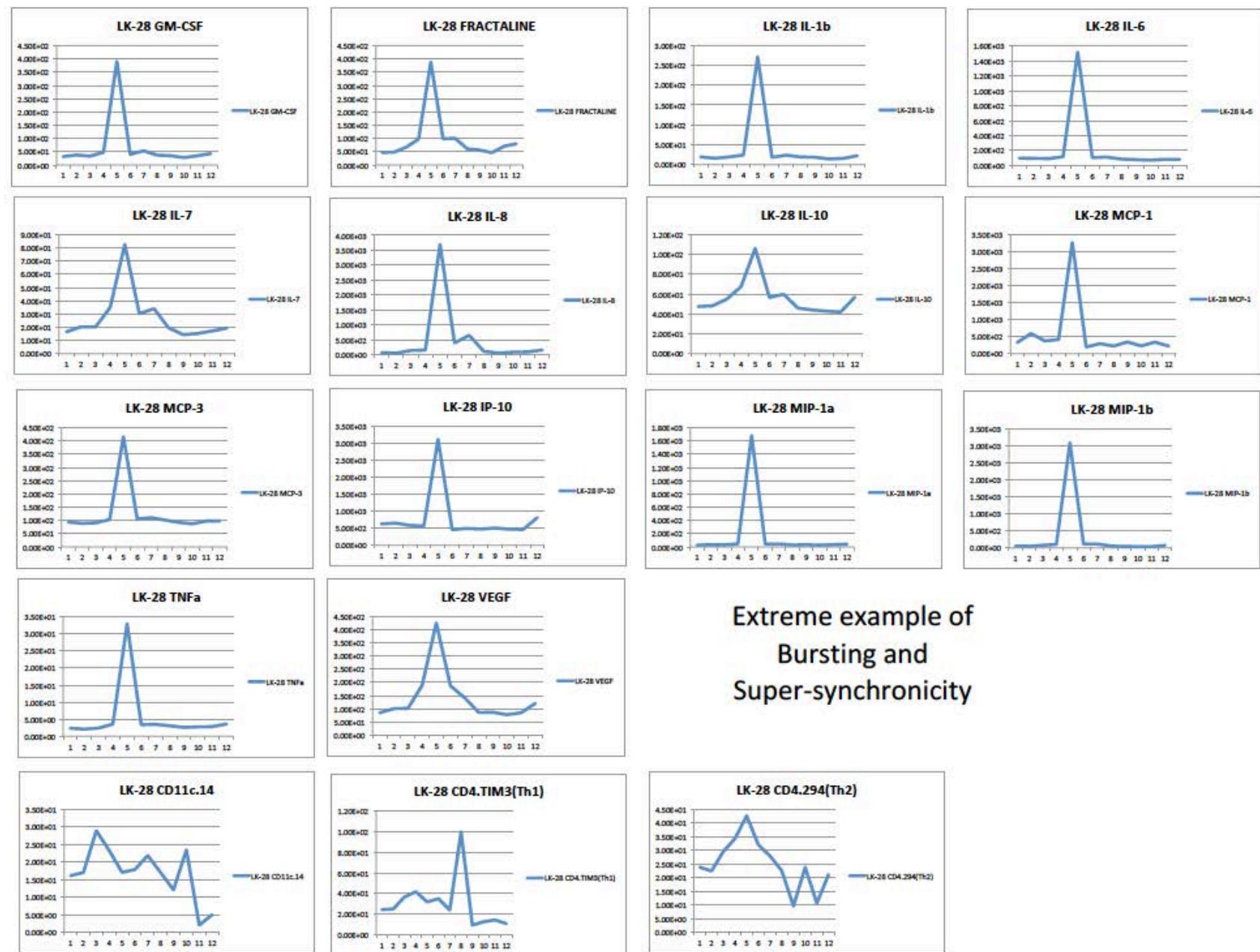
Negative values imply cytokine absorption

Statistical analysis mean & variance

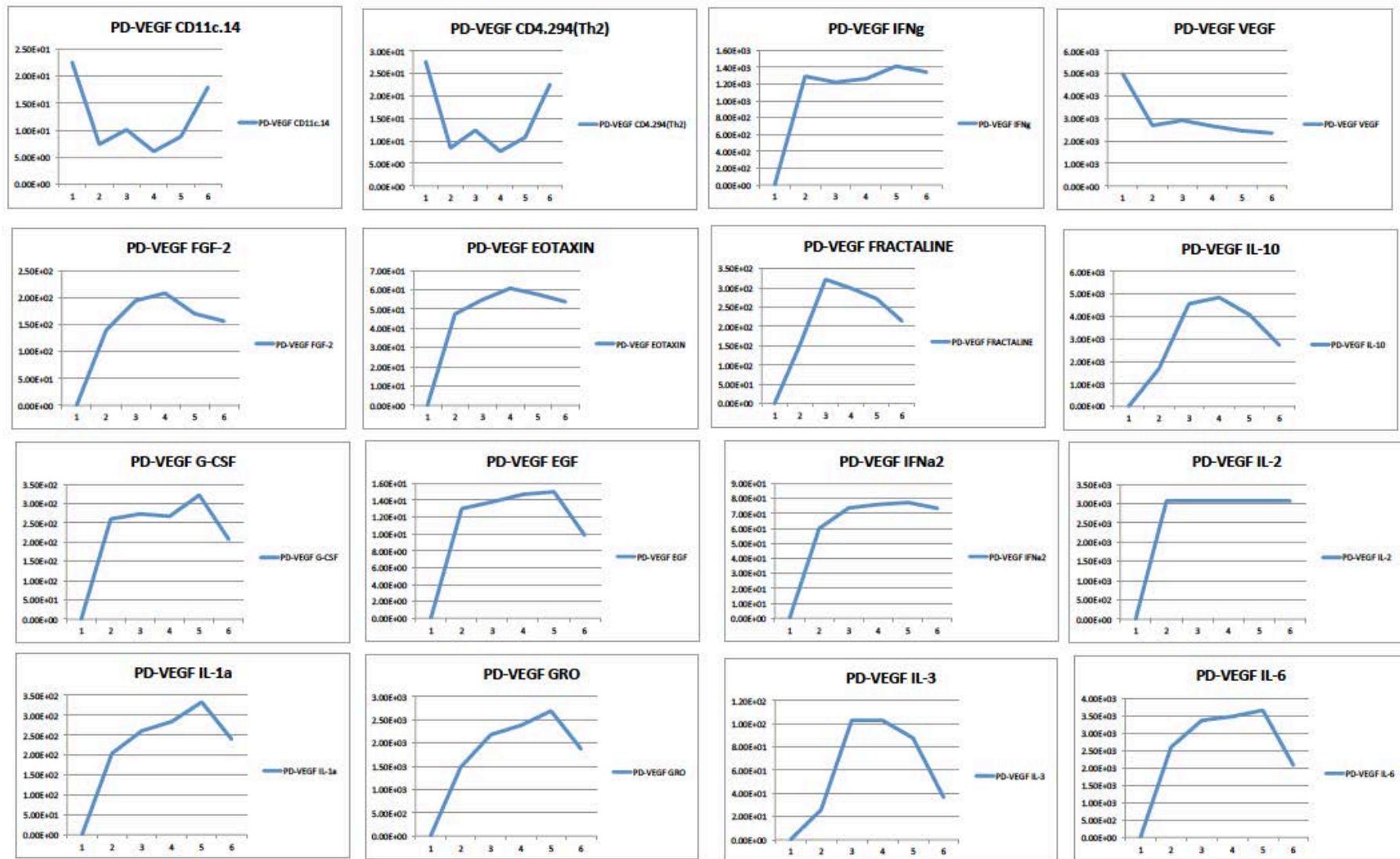
Strong & Weak contributors

- Modulators that impact cellular population change
- Causal impact mean & variance values - across all patients and views

	Mean			Variance		
	CD11c_14	CD4.294[Th2]	CD4.TIM3[Th1]	CD11c_14	CD4.294[Th2]	CD4.TIM3[Th1]
EGF	0.56	0.44	0.48	0.68	0.30	0.40
EOTAXIN	1.47	1.44	1.81	6.22	5.82	9.34
FGF-2	0.06	0.03	0.03	0.01	0.00	0.00
FRACTALINE	0.05	0.04	0.03	0.00	0.00	0.00
G-CSF	0.05	0.03	0.05	0.01	0.00	0.01
GM-CSF	0.13	0.13	0.14	0.03	0.05	0.03
GRO	1.45	1.43	1.55	2.16	2.88	2.57
IFNa2	0.08	0.07	0.07	0.02	0.01	0.01
IFNg	0.01	0.01	0.01	0.00	0.00	0.00
IL-10	0.00	0.00	0.00	0.00	0.00	0.00
IL-12p70	0.01	0.01	0.01	0.00	0.00	0.00
IL-13	0.07	0.03	0.01	0.03	0.01	0.00
IL-15	0.02	0.02	0.02	0.00	0.00	0.00
IL-17	0.04	0.04	0.04	0.01	0.01	0.01
IL-1a	0.38	0.19	0.18	0.74	0.09	0.06
IL-1b	0.06	0.06	0.06	0.00	0.00	0.00
IL-2	0.00	0.00	0.00	0.00	0.00	0.00
IL-3	0.00	0.00	0.00	0.00	0.00	0.00
IL-4	0.04	0.02	0.03	0.01	0.00	0.00
IL-5	0.00	0.00	0.00	0.00	0.00	0.00
IL-6	0.08	0.08	0.09	0.01	0.01	0.01
IL-7	0.00	0.00	0.00	0.00	0.00	0.00
IL-8	2.24	2.54	2.40	10.64	15.72	11.79
IL-9	0.00	0.00	0.00	0.00	0.00	0.00
IP-10	1.52	1.23	0.90	2.11	0.89	0.50
MCP-1	1.25	1.16	1.01	1.72	1.02	0.57
MCP-3	0.03	0.02	0.02	0.00	0.00	0.00
MDC	1.78	1.57	1.84	4.16	3.30	4.58
MIP-1a	1.17	0.81	1.05	2.58	0.81	2.32
MIP-1b	0.60	0.60	0.50	0.45	0.32	0.18
PDGF-AA	2.09	1.99	2.87	6.12	4.48	7.41
PDGF-AA/A8	2.93	3.42	4.19	16.04	18.96	15.54
RANTES	4.97	5.00	6.33	11.67	15.59	18.24
sCD40L	3.79	3.70	4.53	5.99	6.70	8.58
sIL-2Ra	0.30	0.38	0.31	0.10	0.15	0.13
TGF α	0.01	0.02	0.02	0.01	0.03	0.02
TNF α	0.07	0.02	0.04	0.14	0.01	0.01
TNF β	0.07	0.04	0.04	0.16	0.04	0.03
VEGF	0.20	0.22	0.20	0.02	0.02	0.01



Extreme example of
Bursting and
Super-synchronicity



Examples of Non-linear
Rhythmic Synchronicity

Statistical analysis

Pearson correlation coefficients

- The Pearson correlation coefficient, is sensitive only to a linear relationship between two variables. Other measures exist for the non-linear relations.
- By computing the Pearson correlation coefficient with a signal and a delayed signal we can extract a delayed linear relationship; i.e. Cytokine communication response X-talk.
- Example (next slide): Pearson correlation coefficients show the degree that Cellular CD11c.14, CD4.294(Th2) and CD4.TIM3(Th1) growth modulators work together.
 - The statistics spans all patients, all cellular modulation growth views and all associated growth inducing bio-actions.
 - Highlighted are correlations greater than .75

Cytokine X-talk relationship strength & the Modulation of Cellular growth

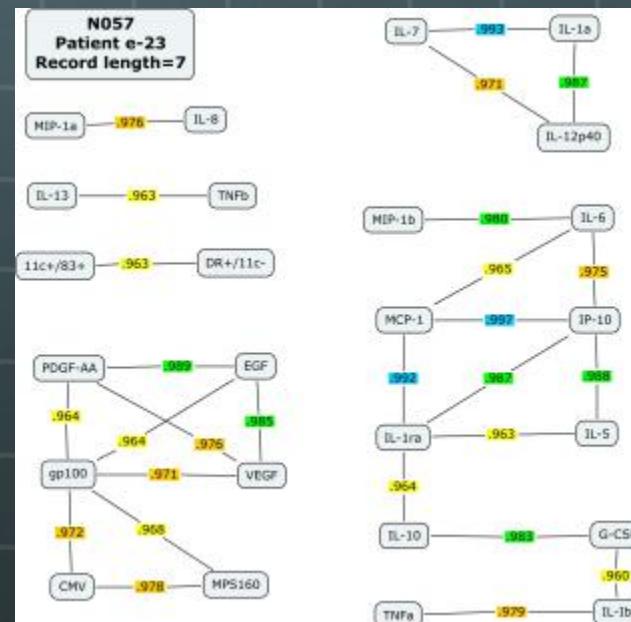
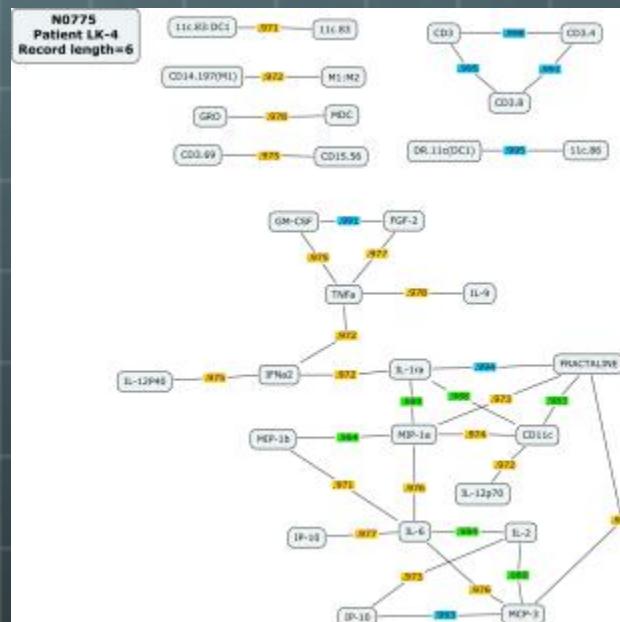
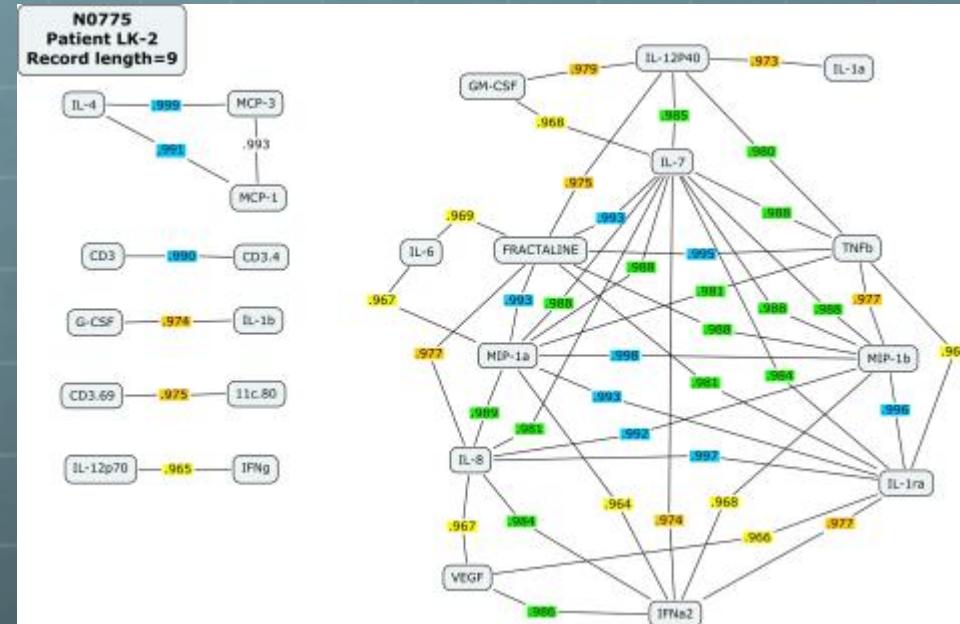
CD13c-34	EGF	EDTAxIN	GM-CSF	GRO	IFN α 2	IL-1 α	IL-6	IL-8	IP-10	MCF-1	MDC	MIP-1 α	MIP-1 β	PDGFA	PDGFA/A/B	RANTES	SC1040	sIL-2R α	VEGF
EGF	1.00																		
EDTAxIN	-0.63	1.00																	
GM-CSF	-0.22	-0.23	1.00																
GRO	0.44	-0.32	-0.32	1.00															
IFN α 2	0.42	-0.42	0.59	-0.44	1.00														
IL-1 α	0.76	-0.50	0.22	-0.15	0.89	1.00													
IL-6	-0.26	-0.07	0.00	-0.45	0.19	0.10	1.00												
IL-8	0.21	-0.17	-0.35	0.94	-0.65	-0.40	-0.47	1.00											
IP-10	0.87	-0.25	-0.24	0.22	0.49	0.82	0.82	-0.15	0.00	1.00									
MCP-1	0.15	0.49	-0.58	0.56	0.86	0.67	-0.59	0.71	-0.16	1.00									
MDC	0.15	0.63	-0.69	0.09	-0.31	-0.06	-0.36	0.06	0.39	0.58	1.00								
MIP-1 α	-0.43	0.44	-0.30	-0.40	-0.15	-0.16	0.79	-0.38	-0.16	0.64	0.14	0.17	1.00						
MIP-1 β	-0.07	0.10	-0.43	0.71	-0.71	-0.50	-0.05	0.81	-0.12	0.66	0.88	0.13	0.19	1.00					
PDGFA	-0.13	0.66	-0.57	0.06	-0.48	-0.36	-0.41	0.07	-0.01	0.39	0.07	-0.14	0.46	0.41	0.78	1.00			
PDGFA/A/B	-0.37	-0.07	0.61	-0.07	0.14	-0.17	0.00	-0.16	-0.49	-0.22	-0.37	-0.06	0.01	0.05	1.00				
RANTES	-0.33	0.20	0.17	0.38	-0.33	-0.46	-0.31	0.31	-0.41	0.39	0.07	-0.14	0.46	0.51	0.42	0.82	1.00		
ICAM1	-0.15	0.16	-0.26	0.69	-0.67	-0.58	-0.38	0.68	-0.29	0.69	0.24	-0.06	0.80	0.51	0.42	0.74	0.59	1.00	
sIL-2R α	-0.13	-0.33	0.44	0.53	-0.17	-0.33	-0.32	0.52	-0.42	0.17	-0.47	-0.52	0.39	-0.20	0.67	0.74	0.59	1.00	
VEGF	0.37	-0.29	-0.54	0.86	-0.62	-0.31	-0.48	0.87	0.06	0.65	0.18	-0.35	0.65	0.24	-0.19	0.20	0.66	0.32	1.00
CD4-294(Th2)	EGF	EDTAxIN	GM-CSF	GRO	IFN α 2	IL-1 α	IL-6	IL-8	IP-10	MCF-1	MDC	MIP-1 α	MIP-1 β	PDGFA	PDGFA/A/B	RANTES	SC1040	sIL-2R α	VEGF
EGF	1.00																		
EDTAxIN	-0.34	1.00																	
GM-CSF	-0.73	-0.18	1.00																
GRO	0.72	-0.11	-0.47	1.00															
IFN α 2	-0.77	-0.20	0.93	-0.73	1.00														
IL-1 α	0.01	-0.49	0.19	-0.49	0.45	1.00													
IL-6	-0.25	0.25	-0.22	0.02	-0.22	-0.30	1.00												
IL-8	0.75	-0.11	-0.46	0.91	-0.71	-0.37	0.00	1.00											
IP-10	0.62	0.18	-0.68	0.36	-0.54	-0.22	0.01	0.47	1.00										
MCP-1	0.47	0.57	-0.69	0.49	0.75	-0.37	-0.09	0.47	0.70	1.00									
MDC	0.36	0.71	-0.72	0.33	-0.72	-0.49	-0.02	0.30	0.48	0.86	1.00								
MIP-1 α	-0.51	0.53	-0.16	-0.45	0.00	-0.09	0.63	-0.51	0.06	0.17	0.19	1.00							
MIP-1 β	0.56	-0.01	-0.47	0.92	-0.69	-0.45	0.34	0.90	0.38	0.43	0.28	-0.20	1.00						
PDGFA	0.07	0.83	-0.46	0.07	-0.42	-0.32	-0.11	0.05	0.41	0.82	0.91	0.33	0.08	1.00					
PDGFA/A/B	-0.43	-0.13	0.67	0.06	0.48	-0.19	-0.20	-0.06	-0.55	-0.21	-0.39	-0.06	0.04	-0.18	1.00				
RANTES	0.18	-0.13	0.08	0.63	-0.14	-0.29	-0.04	0.57	-0.08	0.17	-0.02	-0.27	0.70	0.02	0.67	1.00			
ICAM1	0.60	0.00	-0.46	0.90	-0.69	-0.46	-0.01	0.82	0.40	0.85	0.39	-0.17	0.84	0.25	0.26	0.74	1.00		
sIL-2R α	0.43	-0.30	0.04	0.84	-0.27	-0.42	-0.20	0.79	-0.08	0.12	-0.09	0.65	0.73	-0.17	0.48	0.83	0.74	1.00	
VEGF	0.92	-0.23	-0.75	0.89	-0.87	-0.34	-0.07	0.80	0.43	0.52	0.45	0.39	0.70	0.11	-0.27	0.32	0.75	0.56	1.00
CD4-TIM3(Th3)	EGF	EDTAxIN	GM-CSF	GRO	IFN α 2	IL-1 α	IL-6	IL-8	IP-10	MCF-1	MDC	MIP-1 α	MIP-1 β	PDGFA	PDGFA/A/B	RANTES	SC1040	sIL-2R α	VEGF
EGF	1.00																		
EDTAxIN	0.19	1.00																	
GM-CSF	0.87	-0.19	1.00																
GRO	0.29	-0.15	-0.54	1.00															
IFN α 2	-0.68	0.38	0.61	-0.62	1.00														
IL-1 α	0.52	0.74	-0.50	0.28	0.25	1.00													
IL-6	0.00	0.22	-0.10	-0.08	0.50	0.59	1.00												
IL-8	0.64	-0.11	-0.38	0.87	-0.78	-0.07	-0.35	1.00											
IP-10	0.75	0.60	-0.68	0.85	-0.45	0.49	-0.08	0.66	1.00										
MCP-1	0.87	0.38	0.75	0.78	-0.63	0.39	-0.31	0.63	0.86	1.00									
MDC	0.66	0.82	-0.71	0.52	-0.16	0.71	0.04	0.23	0.86	0.80	1.00								
MIP-1 α	-0.17	0.21	0.00	-0.32	0.65	0.52	0.95	-0.61	-0.27	-0.42	-0.02	1.00							
MIP-1 β	0.45	-0.25	-0.21	0.80	-0.61	-0.13	-0.07	0.90	0.50	0.33	-0.01	-0.35	1.00						
PDGFA	0.64	0.61	-0.62	0.59	-0.32	0.46	-0.26	0.31	0.81	0.88	0.89	-0.28	0.05	1.00					
PDGFA/A/B	-0.17	0.37	0.27	0.32	0.01	0.04	-0.01	0.13	0.04	0.04	0.07	0.13	0.28	1.00					
RANTES	0.25	0.25	-0.04	0.58	-0.13	0.13	-0.25	0.38	0.52	0.42	0.34	-0.31	0.39	0.61	0.74	1.00			
ICAM1	0.72	0.31	-0.47	0.93	-0.37	0.46	0.08	0.66	0.81	0.72	0.57	-0.11	0.64	0.67	0.51	0.74	1.00		
sIL-2R α	-0.27	-0.36	0.49	0.34	-0.15	-0.61	-0.31	0.45	0.02	-0.12	-0.40	-0.41	0.62	-0.15	0.60	0.48	0.28	1.00	
VEGF	0.77	-0.29	-0.61	0.86	-0.94	0.12	-0.35	0.85	0.57	0.73	0.25	-0.58	0.71	0.41	-0.08	0.24	0.59	0.25	1.00

Pearson Correlation Coefficients

- Show Synchronicity wiring diagrams
- Show Orthogonality of Effect (measured) vs. Effect (computed per Causal Impact)
- Orthogonality implies long term damping
- Feeding off of very small nutation instability studies; e.g., thermally induced instabilities
 - Identify the negative damping cause
 - Looks promising but not yet there

Bio-observable Synchronicity wiring-diagrams

Examples of Patient Bio-variability



Control dynamics



Aerospace

- Continuous or discrete error signal generated
- Requires the math operation of “subtraction”
 - Error equals desired minus actual
- Control system commands action that will drive observed error signal to zero
- Active control ends when error signal stops
- Adaptive control founded on
 - Parameter estimation



Immuno control

- No concept of “error signal”
- No Math operation of “subtraction”
- Has “decision making” measures
 - Self-organization
 - Start/end task
- Has Logistics subsystem
 - Manages flow of mass, energy and signaling resources to meet Immuno control needs
- Control parameters undefined
- Control subsystems interwoven

Feedback control vs. Process decision making

- Aerospace
 - Mode control
 - Well defined rules
 - Feedback control
 - Well defined error and command signals
 - Linear process with non-linear contributions
- Immuno-biology
 - Bio-action event control
 - Patient variability
 - Many concepts support decision making process
 - “Swarm intelligence”
 - Ants, honeybees, locusts, termites, birds, fish, etc.
- Bio-chemical process
 - Rules unclear
 - Parameters unclear
 - Extensive networking
 - Multi-use & redundancy
 - Foundationally non-linear process

Decision making signal detection & duration

- Linear electo-mechanical systems
- Addition and subtraction of linear signals
 - Comparable strength
- Many data samples per highest frequency of importance
- Non-linear bio-system
- Addition and subtraction of non-linear (triple-product) signals
 - Significant amplification above linear signal strength
- **Maybe:** Re. coarse data
 - Via DNA rules and triple products amplify/suppress essence of sensed data
 - Self-organization concept
- **Maybe:** Re. Limited memory duration
 - process focused within a sliding window of relevance.

Swarm intelligence & Modes bio-action



Ants



Self-organization



Chemotaxis (Search & destroy)



Diversity of knowledge



Robust decision making (Bio-action event triggering)



Bees



Indirect collaboration



Timely reaction of bio-action event sources to invasion



Termites



Bird flocks



Adaptive mimicking



Massive coordination of Immuno defense options



Dark side



Immuno defense destabilization



Locusts

Cellular decision making & “Honeybee Democracy”*

- Cells have many bio-functions
- Bio-function action level requires decision making
- Microenvironment is probed
- Observable (unknown) decision making parameters are reported to cellular receptors
 - Pathways from receptors to nucleus for data processing exist
- Causal impact data reveals response consistent with low level probing ending with bio-action
- Swarm intelligence & emergent behavior
- Honeybee colonies perform many tasks
- Honeybee task performance requires decision making
- Near nest environment is probed
- Observable decision making parameters are reported to colony via “dance”
- Consensus based decision is made and acted upon
- Swarm intelligence & emergent behavior

Task scheduling in Immuno control dynamics

- Task control concept thoughts:
 - Task is triggered
 - Task is maintained
 - Task is stopped
- Logistics control
 - Supports task activity
 - Delivers to task source
 - Energy packets
 - Construction material
 - Activity control signals
 - Delivers task source products to
 - Task's support target micro-environment
- Decision making for
 - Task triggering
 - Task stopping
- Logistics required for
 - Task maintenance
 - Gathers and delivers task maintenance necessities to activity micro-environment
 - Delivers products of task to Logistic subsystem for distribution and delivery
- Task activity
 - Well scripted sequences of (resource limited) biochemical actions and reactions

Immuno-control breakdown

- ➊ Via Causal impacts discover organizational hierarchy
 - ➌ Organizational groups are networked
- ➋ Via Bio-expert knowledge base + Causal impact data
 - ➌ Infer Immuno-control system breakdown and networking
 - ➌ Identify potential points for clinical intervention
- ➌ Via correlation & statistical analysis
 - ➌ Identify key enablers of tasks
 - ➌ Identify natural behaviors and participants
 - ➌ Link tasks with enablers
 - ➌ Associate to clinical relevance

Physical cosmology and Quantum mechanics

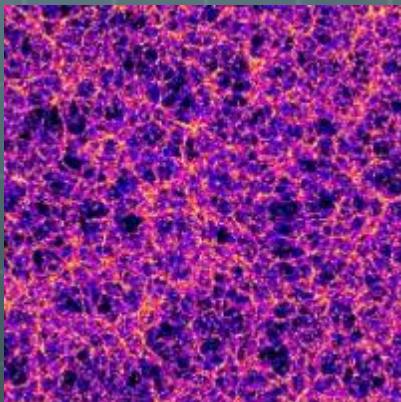
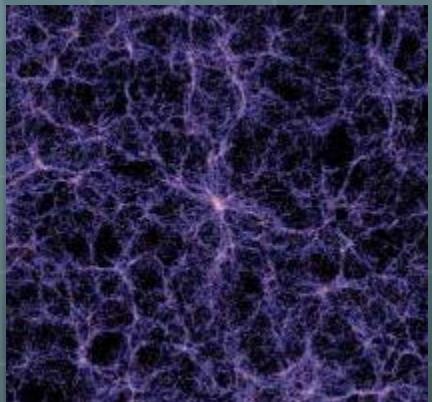
Searching for ideas to borrow

- Remove observed all sky mapping background, what happens long term
- Quantum information and computation
- Variables of state – position, spin, momentum
- Searching for bio-matter - need to reflect “Size” relative to:
 - production & absorption
 - stimulation & suppression
- Searching for generic rules that cross patient bio-variability
- Remove short term transient Immuno response, what happens long term
- Immuno communication via concentration gradients & neural computation
 - Beyond binary logic
- Variables of state – populations of effect, source, trigger, modulator
- Can't get to certainty
 - Massively: robust, redundant and adaptable
- Synchronicity & self-organization

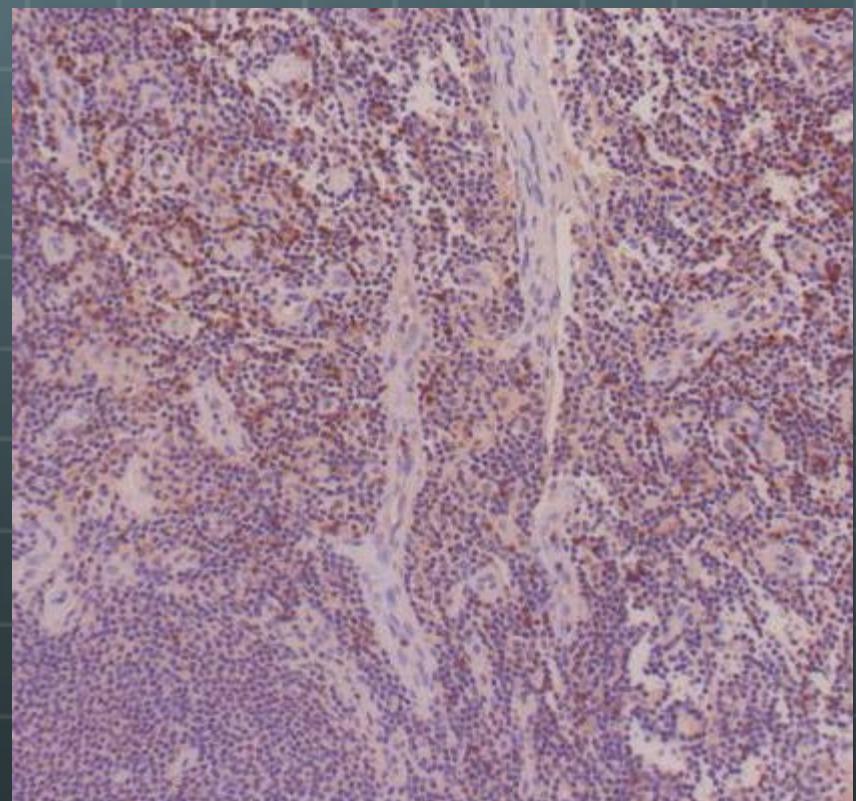
Very new - Physical Cosmology

Dark Matter-Energy vs. Dark bio-stuff gradients

Galactic filaments



Tumor cellular image



Multi Spectral imaging

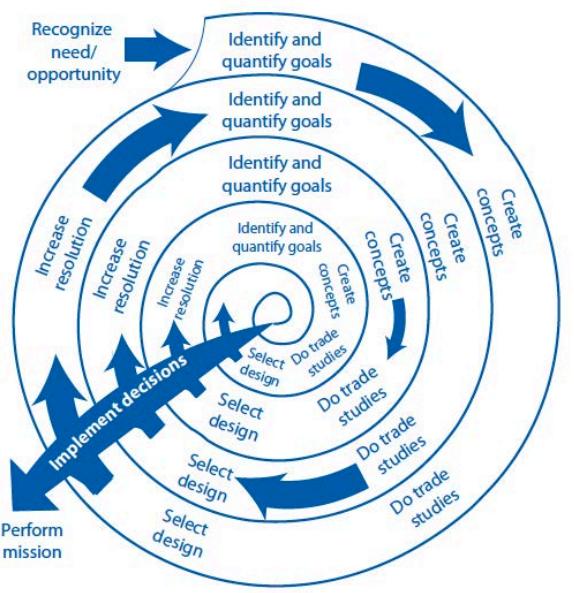


Proposal submitted by

Midwest Melanoma Partnership

- Clinical trial 30 patients with metastatic melanoma
- Ipilimumab (IPI) Immunotherapy treatment for 12 weeks
 - Treatment on weeks 1,3,6,9: Blood drawn weekly
 - Tumor biopsies & imaging on weeks 1,6,12
- All data to be used to reverse engineer Immuno control dynamics in Tumor microenvironment (TME)
 - Compare analysis results across all patients
 - Identify statistically meaningful correlations between all Effects measured and all population changing Causal impacts
 - Perform focused experimental validation Petri dish tests
 - Perform Clinical validation of new understandings
 - Apply Cause-effect understanding of IPI & patient's Immuno control dynamics response within the TME

Patience + Understanding = Progress



Actions have Reactions



Patience + Understanding = Progress

