Systems approach to immuno-oncology (IO) drug development: Integrating Data and Knowledge

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Background and Objectives

Immunotherapy is hailed as the future of cancer therapy as it facilitates the host's own immune system to fight the cancer. Immune check point inhibitors such as anti-PD1/PDL1, CTLA-4 have shown good clinical efficacy in a number of cancer trials. Some of the major challenges in Immuno-oncology (IO) field is keeping up with rapidly disseminated scientific and clinical trial literature and lack of direct comparison of therapies across trial. Understanding why some patients respond and others don't to IO therapy and what combinations of drugs are likely to increase response are critical concerns. Here we propose systems approaches to tackle these problems by integrating data and knowledge using Network meta-analysis (NMA) and Quantitative systems pharmacology (QSP) modeling[1].

Data Assimilation: Immuno-Oncology Knowledgebase (IO-Kb)

Vantage Research's IO-Kb is a in-house curated database of about 70 clinical trials, conducted from 2010 to 2018, comprising of over 21,645 patient data with access to about 10 immunotherapies across various solid cancers.

Data Integration: Network meta-analysis (NMA)

Network Meta-Analysis (NMA) is a potent method which helps in comparing multiple interventions for the same disease across same outcomes. This mixed treatment meta-analysis borrows strength from both direct and indirect evidences to project certainties about treatments and applicable combinations. The biggest merit of the methods is that it allows for estimation of comparative efficacy that have not been investigated head to head in randomized clinical trials.

11 unique clinical trials comparing checkpoint inhibitors and combinations with chemotherapies were selected. Risk of bias and quality of the selected studies were evaluated using GRADE-pro and Cochrane guidelines. Analysis is done using "R" "gemtc" package. Heterogeneity in the data was checked with a random effects model and node-splitting analysis was done to check for inconsistency in the network. SUCRA scores were calculated from the Rankograms to rank the nodes in the network (Figure 1 & 2).

Based on the observations from the 3 clinical outcomes Pembrolizumab shows good efficacy, higher proportion of 6 months PFS and manageable tolerability among all the therapies compared. Systematic analyses such as these are necessary to digest rapidly generated clinical trial data in new fields such as Immunotherapy to make rational decisions in comparing therapeutic outcomes.

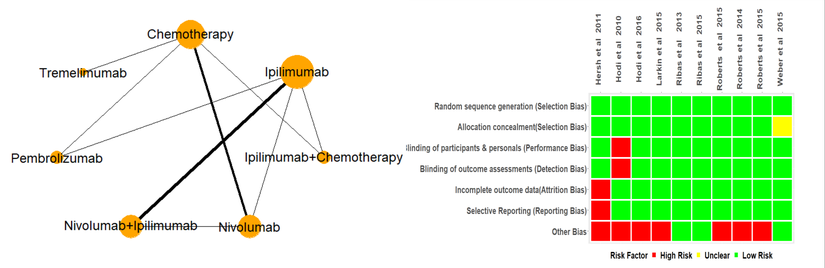


Figure 2: A) Network for Objective Response Rate (ORR); B) Evidence Risk Bias analysis

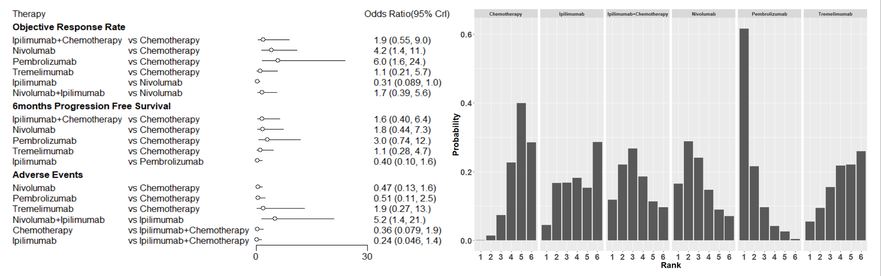


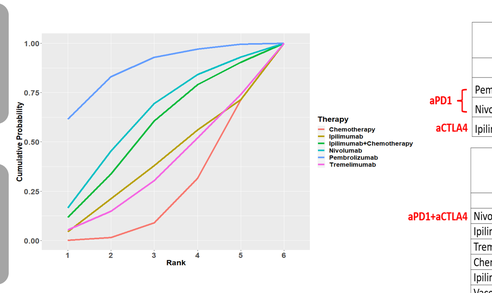
Figure 2: C) Forest Plot for clinical endpoints; D) Rankograms for selected therapies

Step 1
Defining Research Scope, Objective and finding evidence for analysis
1. What is the objective and scope of this analysis ?
2. How are clinical trials selected for analysis ?
3. Network diagrams from the selected data

Step 2
Examining the strength of evidence
1. Evaluating the risk of bias in selected studies
2. Network geometry analysis
3. Heterogeneity and Inconsistency check for networks

Step 3
Results and Interpretation of Network Meta Analysis
1. Summarising therapy effect estimates in to a Forest plot
2. Rankogram from Forest plot
3. SUCRA scores for ranking therapies

Figure 1: A Flow chart explaining Key Steps in Network Meta-analysis



	Therapies	ORR network SUCRA	ORR network Rank	AE network SUCRA	AE network Rank	PFS network SUCRA	PFS network Rank
aPD1	Pembrolizumab	83	2	75	2	87	1
aPD1	Nivolumab	69	3	80	1	61	2
aCTLA4	Ipilimumab	27	5	65	3	38	4

	Therapies	ORR network SUCRA	ORR network Rank	AE network SUCRA	AE network Rank	PFS network SUCRA	PFS network Rank
aPD1+aCTLA4	Nivolumab+Ipilimumab	89	1	11	9	NA	
	Ipilimumab+Chemotherapy	46	4	17	8	55	3
	Tremelimumab	22	6	29	7	36	5
	Chemotherapy	14	7	47	6	23	6
	Ipilimumab+gp100	NA		63	4	NA	
	Vaccine	NA		62	5	NA	

Figure 2: E) Surface Under the cumulative Ranking (SUCRA) Curve score; F) Table summarizing SUCRA score and Ranks for selected therapies

Data and Knowledge Integration: IO-QSP modelling

- The intent of an IO-QSP model is to integrate knowledge and data from the molecular, cellular, and organ/tissue level interaction with that of population level dynamics using a multi-scale modeling approach (Fig 3).
- Critically, data from multiple scales starting from the "top-down" clinical scale to "bottom-up" scales such as protein-receptor interaction, signalling pathways, interaction between multiple organ systems etc. are used to develop these models. The goal is to quantitatively assess the effect of perturbations in the mechanistic scale on the clinical scale of interest.

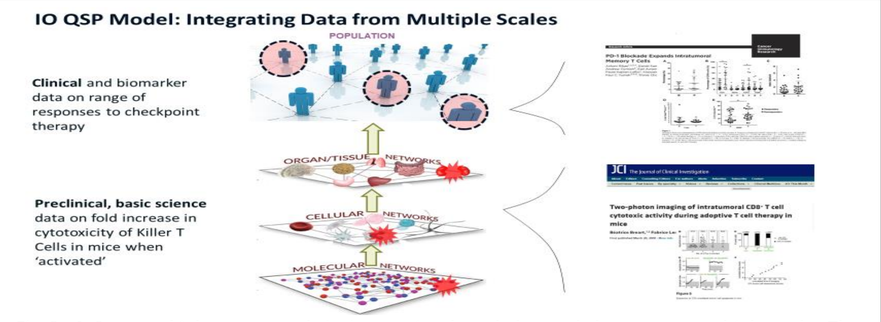


Fig 3: A Systems biology approach in integrating knowledge and data across multiple scale. The disease pathophysiology is derived from basic science, preclinical literature etc. The clinical and biomarker data is used to fit the model. Modified from Alyssa W. Goldman et al., Front. Physiol., 2015[2]

Challenges in IO-QSP modelling

Immuno-oncology is largely unexplored in QSP space due to heterogeneity, and lack of mechanistic understanding of the underlying biology. Heterogeneity in cancer, occurs at various levels (e.g., at the molecular, cellular and population levels) and poses challenges in finding relevant data and modelling (Fig 4A, B, and C).

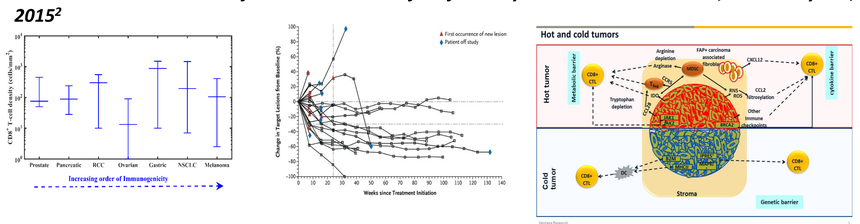


Fig 4A: Density of CD8+ T cells at baseline for different cancers; Fig 4B: **Percent change in tumor diameter from baseline of each individual patient in a clinical trial. From Topalian et al., 2015[3]; *Fig 4C:* Mechanisms involved in tumor immune evasion**

IO-QSP Project Example

At Vantage Research, IO QSP modelling starts with a comprehensive literature survey and analysis of biological data, distilling the contents of relevant public literature to derive a complete model map of tumor immune interaction (Fig 5A). This literature survey is done from a systems physiological perspective. This model map is then translated into a set of ordinary differential equations with reaction kinetics constrained by available data.

As an example, a 3 compartment simple model that encompasses tumor heterogeneity (by assigning different attributes to different compartments) and spatial complexity at its base is shown (Fig. 5B, C). Tumor induced $CD8^+$ T-cell inactivation is assumed in this model and therapy reverts inactivated $CD8^+$ T-cell population to its active state. Figures 5D and 5E shows different baseline patients created from the model simulations via alternate parameterizations and percentage of each baseline category as we vary a single parameter while keeping every other parameter a constant.

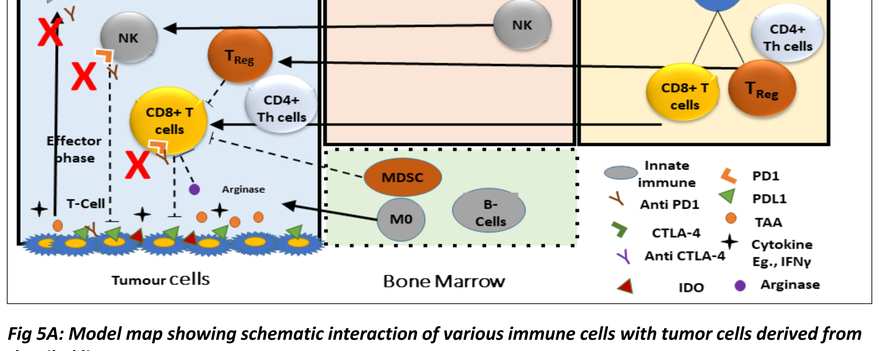


Fig 5A: Model map showing schematic interaction of various immune cells with tumor cells derived from detailed literature survey

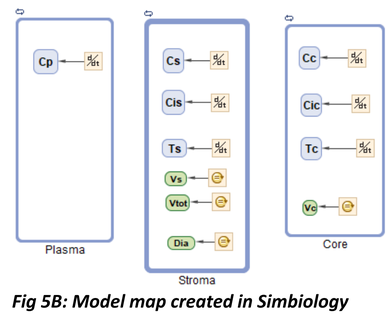


Fig 5B: Model map created in Simbiology

$$\frac{dC_c}{dt} = Trc_s^c(1-Infil)C_s + K_{prol}^c C_c + r_x^c Ci_c - K_{cl}^c C_c - \frac{Ir_c}{V_c} C_c T_c$$

$$\frac{dCi_c}{dt} = Trci_s^c(1-Infil)Ci_s - r_x^c Ci_c - K_{cl}^c C_c + \frac{Ir_c}{V_c} C_c T_c$$

$$\frac{dT_c}{dt} = Gr_c T_c\left(1-\frac{T_c}{b}\right) - Trt_c^s T_c - \frac{Kr_c}{V_c} C_c T_c$$

Fig 5C: Model equations in the "Core" compartment

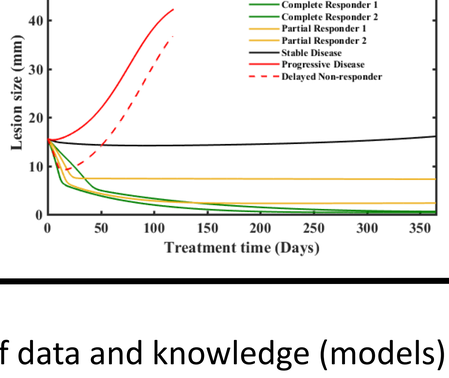


Fig 5D: Baseline VPs generated via alternate parameterizations. Solid green line, Solid yellow line, solid black line, solid red line and dashed red line shows the temporal dynamics of tumor diameter of a complete responder, partial responder, stable disease, progressive disease and delayed non-responder, respectively.

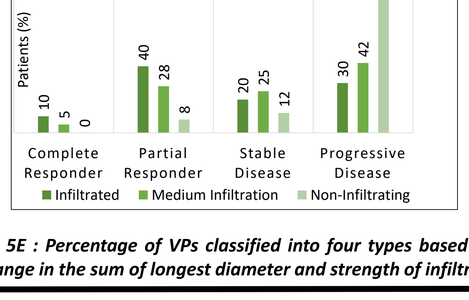


Fig 5E : Percentage of VPs classified into four types based on the change in the sum of longest diameter and strength of infiltration.

Conclusions and Future Directions:

Complex and rapidly evolving field like IO needs large scale integration of data and knowledge (models) across multiple scales to efficiently drive clinical and drug development decision making. Systems approaches such as NMA and QSP approaches are critical tools in this endeavor. Future direction includes, Model based Meta-analysis (MBMA) and incorporating more physiology on to the current mathematical model.

References:

1. Peter K. Sorger et al., An NIH White paper by the QSP Workshop Group, October 2011.
2. Alyssa W. Goldman et al., Front. Physiol., 6 (2015), 225.
3. Suzanne L. Topalian et al., N Engl J Med., 366 (2012), pp. 2443 -54.