Application of a systems pharmacology approach for a detailed investigation of an adverse drug reaction due to distinct mechanisms of immune checkpoint inhibitors

An example of patient-centered reverse translation

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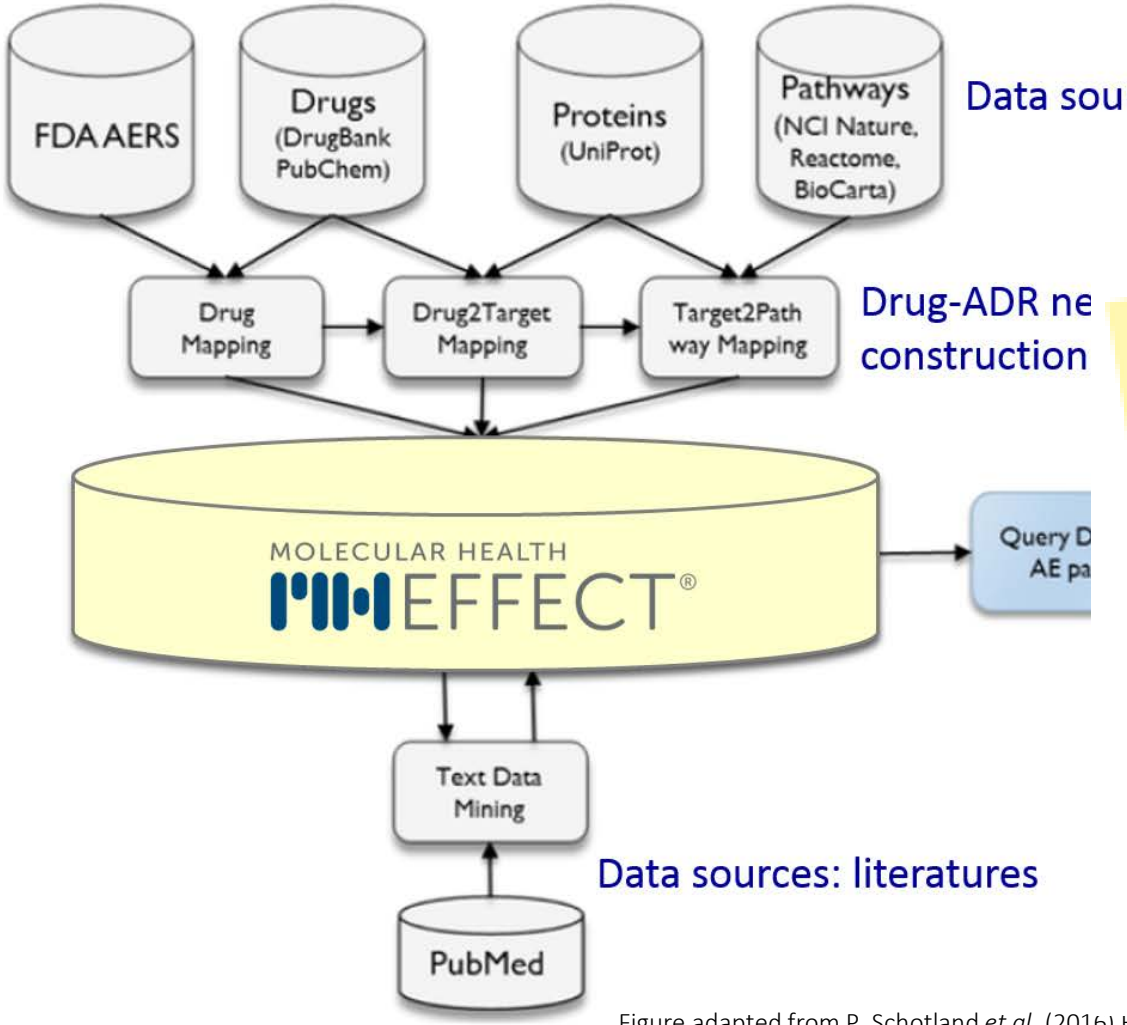
Systems Approach to Drug Safety utilizing Adverse Event Databanks



Using this proposed approach, we hypothesized how mechanistic differences between CTLA-4 and PD-1 affect an ADR by analyzing and linking FAERS data to their molecular pathways and target levels.

Figure adapted from P. Schotland *et al.* (2016) European J Pharmaceutical Sci, 94: 84-92.

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Systems Approach to Analyze Drug-ADR

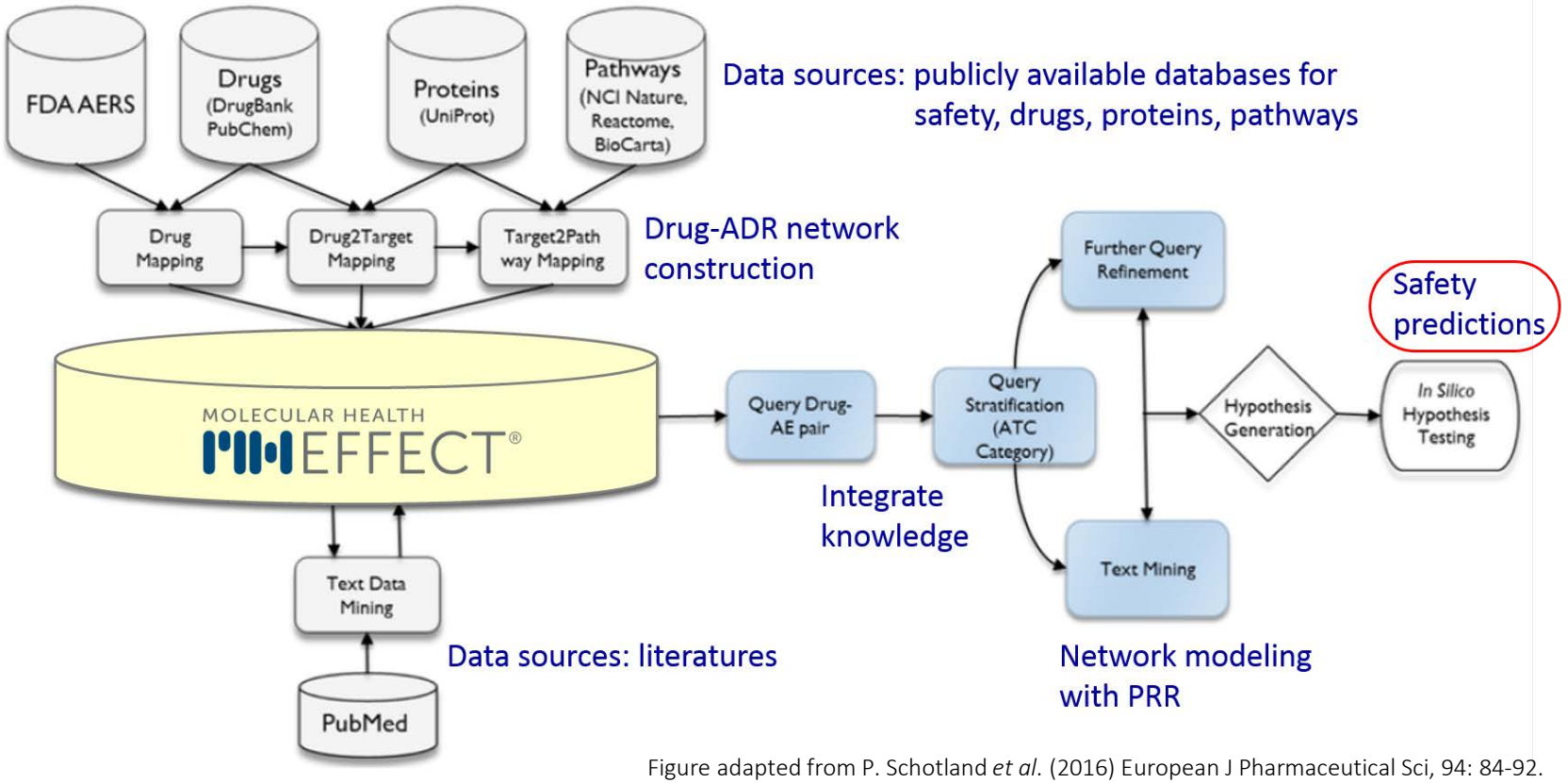


Figure adapted from P. Schotland *et al.* (2016) European J Pharmaceutical Sci, 94: 84-92.

Mapping FAERS to chemical and biological sources integrates knowledge for hypothesis generation towards the underlying molecular pathways and targets of the ADR for safety predictions.

Proportional Reporting Ratio (PRR):

a statistical method used to assess statistical associations between drugs and events of interest using number of case reports

	N w/ event of interest	N w/o event of interest
N w/ drug of interest	a	b
N w/o drug of interest	c	d

N = number of case reports.

$$PRR = \frac{a/(a+b)}{c/(c+d)}.$$

Reference: S.J. Evans *et al.* (2001) Pharmacoepidemiology and Drug Safety, 10(6): 483-486.

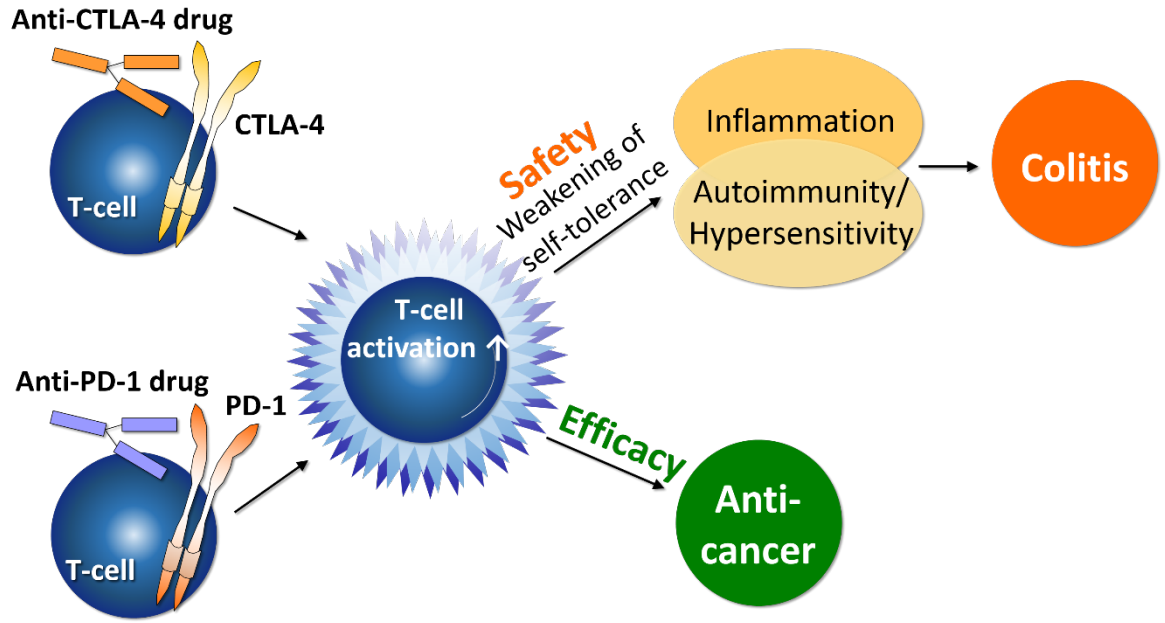
Facts

- Immunotherapy has emerged as a key pillar of cancer therapeutics with the approvals of **ipilimumab**, **nivolumab** and **pembrolizumab**, which inhibit either
  - cytotoxic T-lymphocyte antigen-4 (**CTLA-4**), or
  - programmed death-1 (**PD-1**).

Ipilimumab

Nivolumab & Pembrolizumab

- CTLA-4 and PD-1 are negative regulators of T-cell activation. **Boosting T-cell activation by the immune checkpoint inhibitors** could lead to autoimmunity, leading to ADRs including **colitis**.



Safety Assessment Overview

Cohort	Total N of all ADRs	N of Colitis	PRR for Colitis	95% CI PRR for Colitis
Ipilimumab	5063	411	53.37	48.56 – 58.65
Nivolumab	13990	337	15.72	14.13 – 17.50
Pembrolizumab	5140	72	8.96	7.12 – 11.27
Ipilimumab + Nivolumab	2118	152	46.21	39.61 – 53.91

<u>Drug approval dates</u>

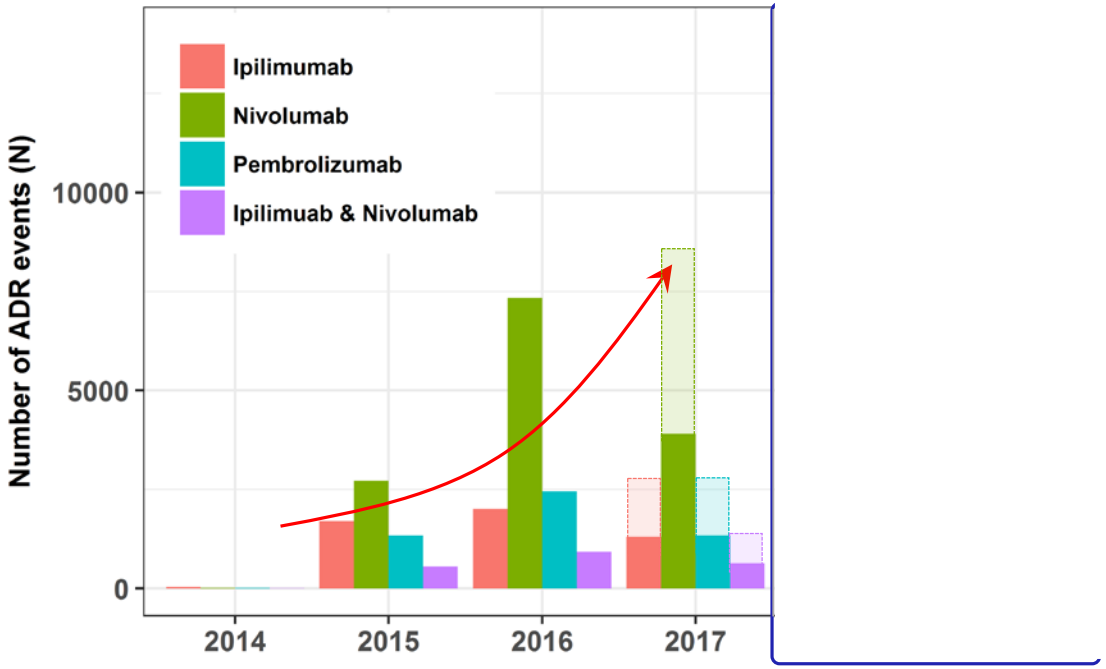
Ipilimumab: 03/25/2011

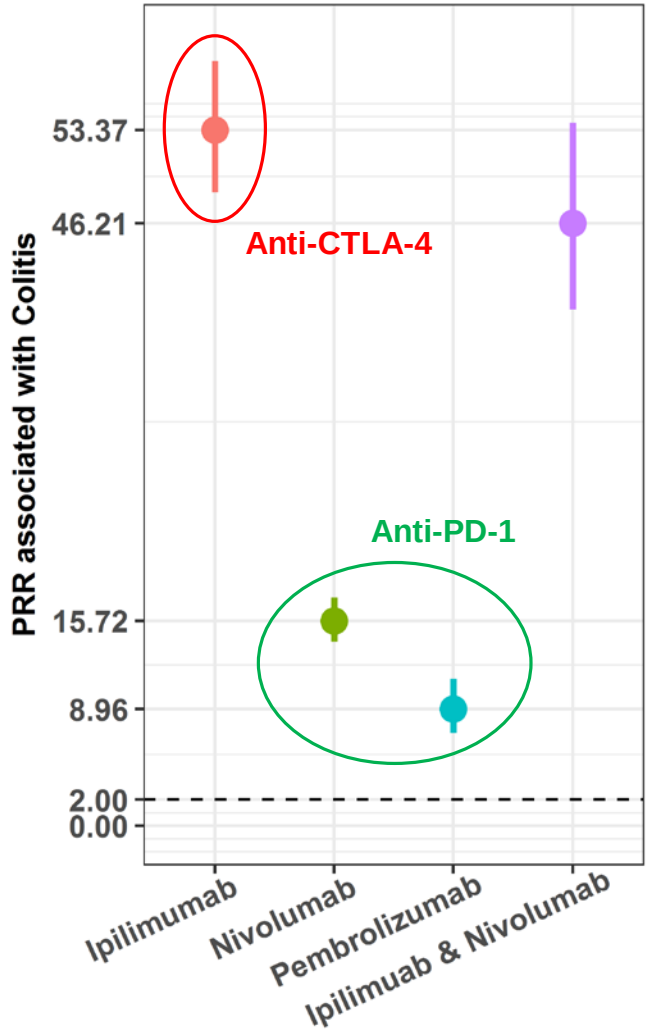
✓ Nivolumab: 12/22/2014

Pembrolizumab: 09/04/2014

<u>Data time frame</u>

12/22/2014 – 06/30/2017





Protein and Pathway Mapping

Pro- and Anti-inflammatory Signaling Pathways

		Cohort	N	PRR	95% CI PRR
Pro-inflammatory signalling (IL6)	Drug	Ipilimumab	133	0.39	0.33 – 0.46
		Nivolumab	348	0.37	0.33 – 0.41
		Pembrolizumab	118	0.34	0.28 – 0.41
		Ipilimumab + Nivolumab	78	0.54	0.44 – 0.68
	Drug + Colitis	Ipilimumab	14	▲ 0.50	0.30 – 0.84
		Nivolumab	21	▲ 0.92	▲ 0.61 – 1.39
		Pembrolizumab	5	▲ 1.03	▲ 0.44 – 2.39
		Ipilimumab + Nivolumab	9	▲ 0.87	▲ 0.46 – 1.65
Anti-inflammatory signalling (IL12)	Drug	Ipilimumab	355	0.67	0.61 – 0.74
		Nivolumab	829	0.57	0.53 – 0.60
		Pembrolizumab	373	0.69	0.63 – 0.76
		Ipilimumab + Nivolumab	215	0.97	0.85 – 1.10
	Drug + Colitis	Ipilimumab	26	▼ 0.60	▼ 0.42 – 0.88
		Nivolumab	30	0.85	0.60 – 1.20
		Pembrolizumab	5	▼ 0.66	▼ 0.28 – 1.55
		Ipilimumab + Nivolumab	14	▼ 0.88	▼ 0.53 – 1.45

Anti-CTLA-4 drug (ipilimumab) is more actively involved in the inflammatory reactions than anti-PD-1 drugs (nivolumab & pembrolizumab).

In the cohorts of 'Drug + Colitis', the PRRs of the pro-inflammatory signaling pathways increased compared to the corresponding cohorts of 'Drug' (▲) while the PRRs of the anti-inflammatory signaling pathways decreased (▼).

Protein and Pathway Mapping

Early Stage of Immune Response related Signaling Pathways

Cohort	N	PRR	95% CI PRR
TCR signaling in naïve CD8+T cells			
Ipilimumab	290	0.66	0.59 – 0.74
Nivolumab	634	0.52	0.48 – 0.56
Pembrolizumab	248	0.55	0.49 – 0.63
Ipilimumab + Nivolumab	188	1.02	0.89 – 1.17
TCR signaling in naïve CD4+T cells			
Ipilimumab	281	0.62	0.55 – 0.70
Nivolumab	641	0.51	0.47 – 0.55
Pembrolizumab	244	0.53	0.47 – 0.60
Ipilimumab + Nivolumab	180	0.95	0.83 – 1.09
Immunoregulatory interactions between a lymphoid and a non-lymphoid cell			
Ipilimumab	216	0.25	0.22 – 0.28
Nivolumab	430	0.18	0.16 – 0.19
Pembrolizumab	172	0.19	0.17 – 0.22
Ipilimumab + Nivolumab	98	0.27	0.22 – 0.32

Anti-CTLA-4 drug (ipilimumab) is more associated with earlier stages of immune response than anti-PD-1 drugs (nivolumab & pembrolizumab).

References:

- Buchbinder and Desai, American J of Clinical Oncology (2016) 39(1): 98-106.
- Fife and Bluestone, Immunological Reviews (2008) 224:166-182.

Discussion and Conclusions

Hypothesis: anti-CTLA-4 drug could induce a more severe rate of colitis than anti-PD-1 drugs due to a greater magnitude of T-cell activation as a result of earlier response of anti-CTLA-4 in the immune response.

What did this systems-based approach provide versus a non-mechanistic approach?

- This systems-based approach provides a process to better map the mechanisms of ADRs to targets and pathways.

Inform drug development pipelines through reverse translation

Acknowledgement

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Thank you very much for your attention!

Dr. Mirjam N. Trame

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Dr. David B. Jackson