ISB M

Immune response template (IRT) database 1.0 brief overview

IRT project team

irt@insysbio.ru

Website: irt.inysbio.ru

Outline

1. Brief overview
2. Types of the schemes
3. Methods of parameters identification
4. IRT application
5. Demo version

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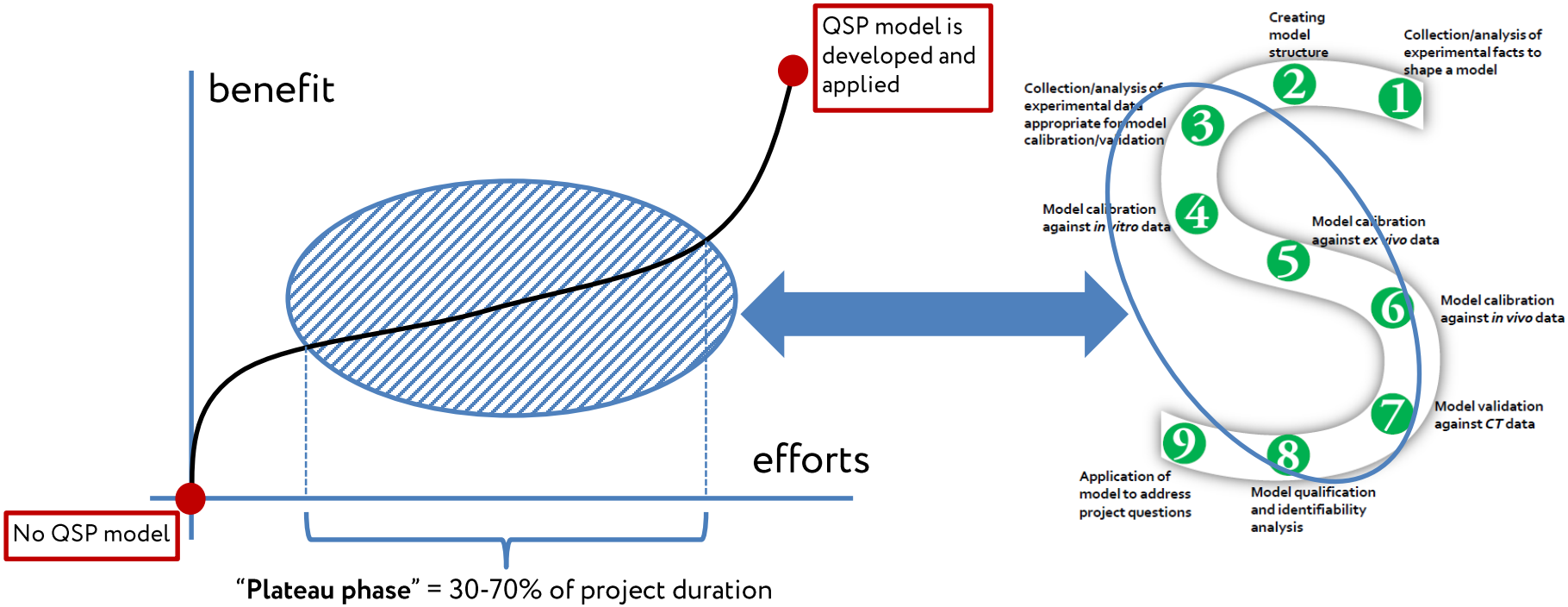
Motivation

Typical duration of QSP projects (0.5 – 1 year) is much longer than PK/PD projects



"**Plateau phase**" includes very important technical steps: collection and processing of data, derivation of rate equations, calibration/validation and qualification of the model.

Is it possible to reduce the duration of the technical steps? How to do it?

The purpose of the work: to demonstrate that such service modeling tool ("template") can be developed for family of related diseases associated with immune response

Key features of Immune Response Template database 1.0

Immune **R**esponse **T**emplate (***IRT***) is a tool for development of QSP models/platforms of different diseases associated with immune response in **human**.

IRT consists of *IRT database 1.0* and *IRT navigator 1.0*.

IRT database 1.0 includes:

- interactive schemes (***passport of immune cell*** and **c*ytokine source profile***) for database navigation
- annotation of each process, cell and cytokine with cross references and links to the external databases
- rate equations of key processes involved in immune response *derived* on the basis of existing knowledge
- values of parameters of the rate equations *identified via fitting* of the specific "in vitro" models against *in vitro* data or calculated using *in vivo* data measured for **healthy human**
- extended annotation of rate equations and parameters

Key features of IRT navigator 1.0

***IRT* navigator** is a tool to access *IRT* database.

IRT navigator provides the intuitive interface for searching the information and model template creation. ***IRT navigator 1.0*** functionality:

- visualization of description and annotation of IRT database components: equations, species, parameters
- access to supplementary materials including files related to in vitro models (used for parameters fitting against in vitro data), files with description of parameters calculation and estimation of initial values for species
- navigation across multiple interactions of immune cells
- automatic generation of model template based on the user selection which can be downloaded as fully annotated *SBML file*

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"Passport" of immune cell

"***Passport" of immune cell*** is a scheme visualizing literature available experimental facts on

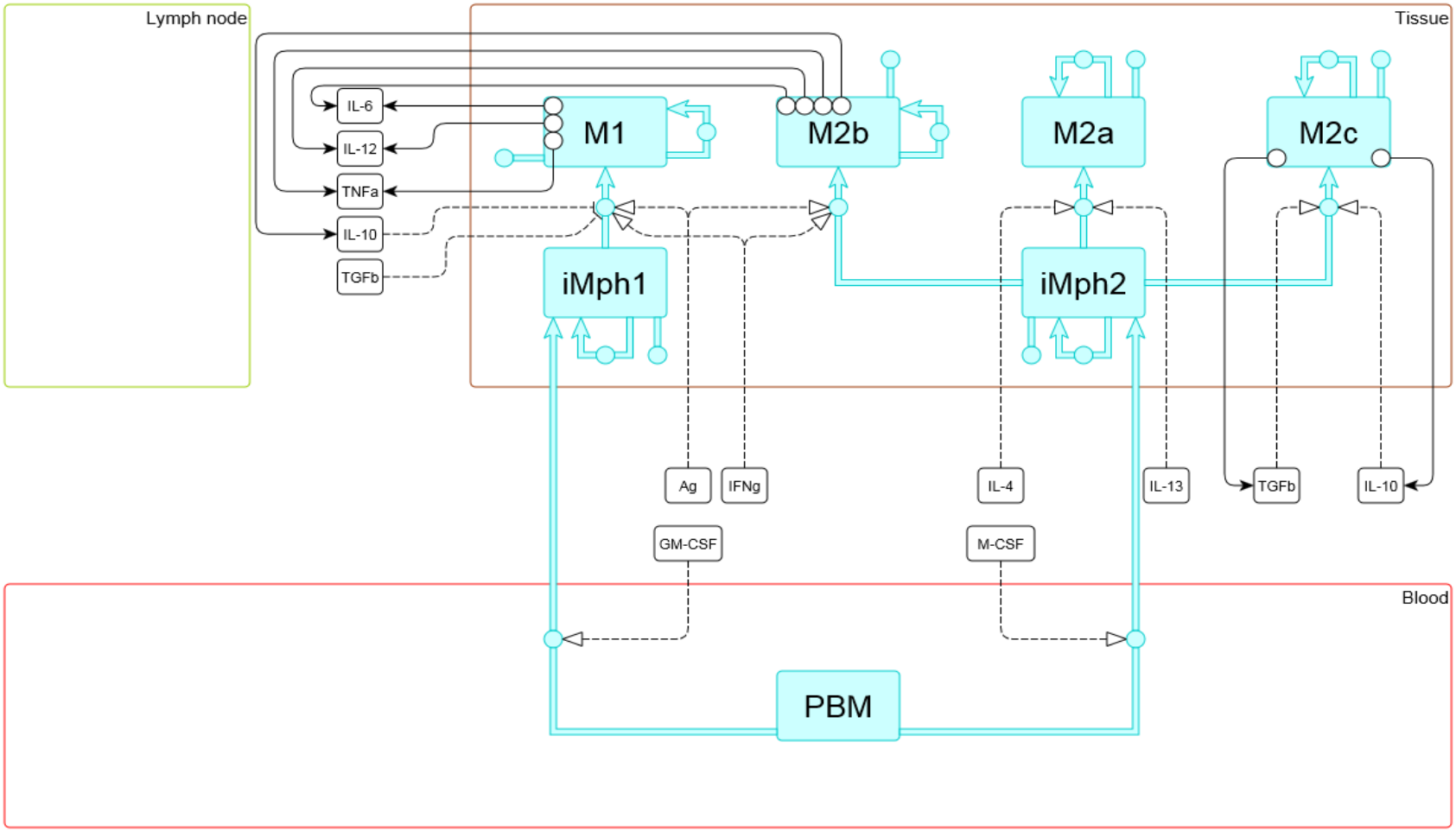
- activation/differentiation and proliferation of the cell
- migration of the cell between blood, lymph node and tissue
- cytokines which are synthesized by this type of cell upon activation
- cytokines/cells that affect this type of cell

Cell	NK	DC	Mph*	PBM**	MDSC	B cells	Th0***	Th1	Th2	Th17	Treg	Naïve CD8 T cells/CTL
Passports	+	+	+	+	+	+	-****	+	+	+	+	+
Rate equations	+	+	+	+	-	+	+*****	+	+	+	+	+
Identified parameters	+	+	+	+	-	+	+*****	+	+	+	+	+

Macrophages; **Peripheral Blood Monocytes; ***Naïve CD4 T cells; ****Th0 cells are presented in cytokine passports of Th1, Th2, Th17 and Treg cells.***Th0 sub-model describes only Th0 apoptosis in vitro; Th0 differentiation into Th1, Th2, Th17 and Treg cells is described in Th1, Th2, Th17 and Treg sub-models.*

“Passport” of immune cell example: macrophages passport

IRT navigator presents macrophages passport in following way



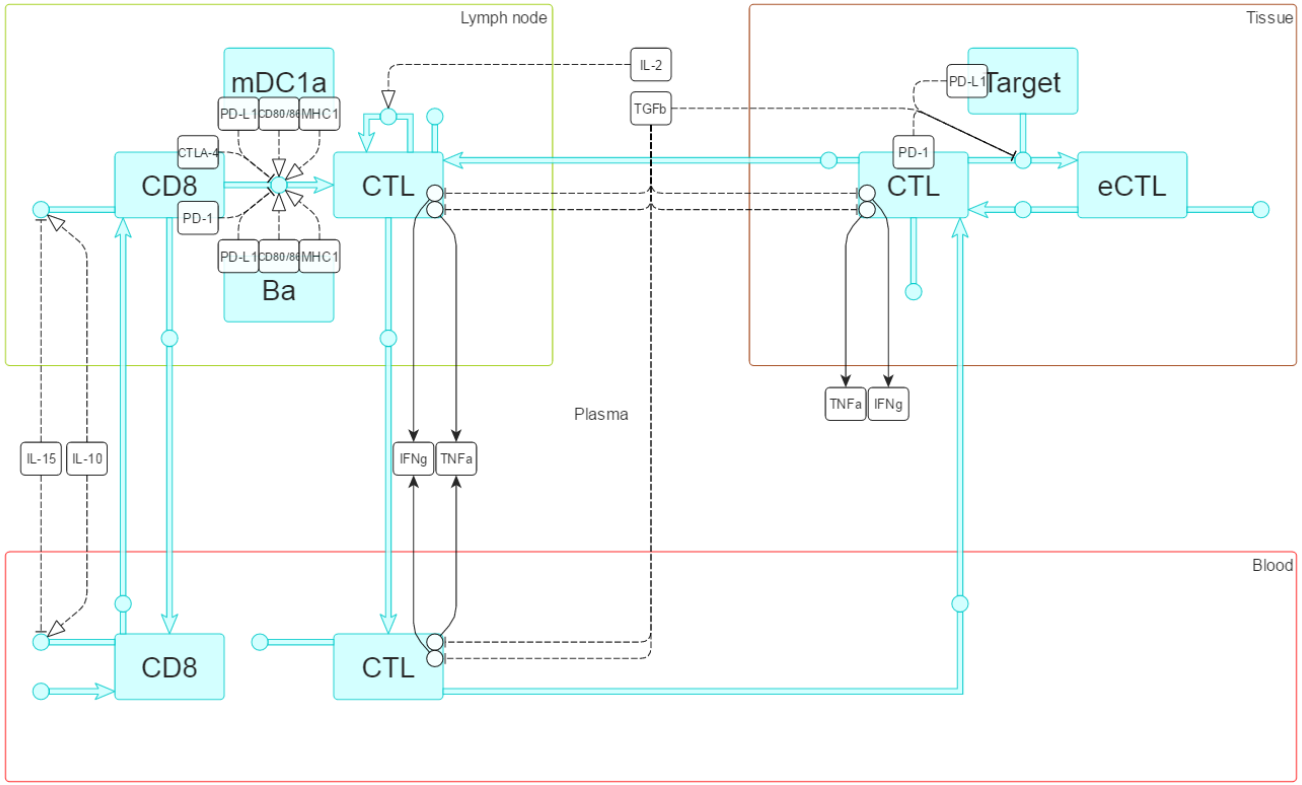
Processes/regulations are supported by data.

"Passport" of immune cell: surface molecules

- Immune cells can directly interact to each other via binding of their **surface molecules**.
- For each process describing direct cell-cell interactions rate equation were derived in such a way to take into account binding of corresponding surface molecules.

Surface molecules	CD3 (Implicitly)	MHC-I	MHC-II	CD28 (Implicitly)	CTLA-4	CD80/86	PD-1	PD-L1	CD40L	CD40 (Implicitly)
Rate equations	+	+	+	+	+	+	+	+	+	+

IRT navigator visualizes surface molecules in ***CTL passport*** in following way:

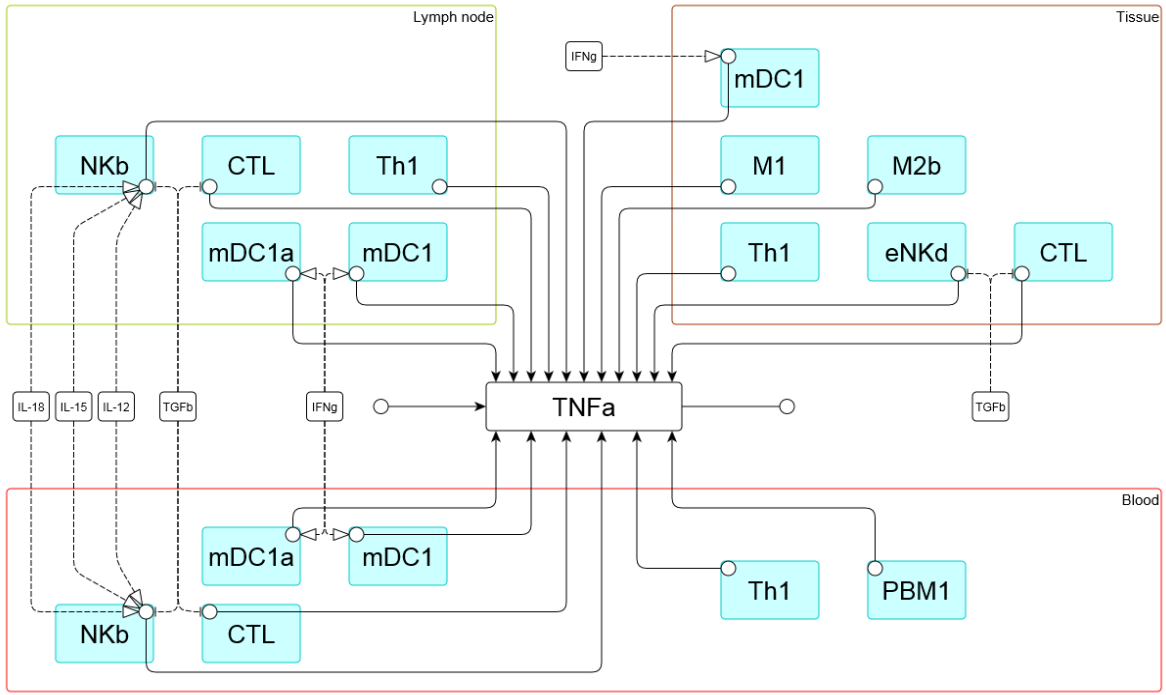


Cytokine source profile

Cytokine source profile is a scheme visualizing literature available experimental facts on

- production of the cytokine by different immune cells located in blood, lymph node and tissue
- regulation of production of the cytokine by other cytokines

IRT navigator presents **TNFa source profile** in following way



Cytokine	GM-CSF	M-CSF	IFNγ	TNFα	TGFβ	IL-1β	IL-2	IL-4	IL-5	IL-6	IL-10	IL-12	IL-13	IL-15	IL-17	IL-18	IL-21	IL-23
Rate equations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Identified parameters	+	-	+	+	-	-	+	+	-	+	+	+	-	+	-	-	-	-

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"In vitro" models for parameter identification

- "In vitro" models describe design of *in vitro* experiments to characterize
- cell differentiation
- proliferation
- cytokines synthesis and their effects on cell dynamics

- Rate equations of the models are derived on the basis of available knowledge on mechanisms underlying corresponding processes

- Parameters of the rate equations are identified against *in vitro* data (**data on immune cells purified from blood of healthy subjects only**)

Files with description of "in vitro" models including model annotation in xls file, model in slv (DBSolve Optimum format) and sbml formats, digitized in vitro data used for model calibration, presentation with model description and quality of calibration will be available for download as supplementary files.

Parameters calculation and initial values for variables

- Parameters describing degradation of cytokines in plasma were calculated using data on cytokines half-life in blood serum/plasma after intravenous infusion in humans

- Parameters describing the concentration of surface molecules (MHC-II, CTLA-4) per one cell were calculated using the data on number of surface molecules on one cell and difference in expression of surface molecules on various states on the cells

- Initial values for variables/species describing immune cells in blood were taken equal to levels in healthy subjects

- Initial values for variables/species describing cytokines in blood plasma were taken equal to levels in healthy subjects

Files with description of all calculations will be available for download as supplementary files.

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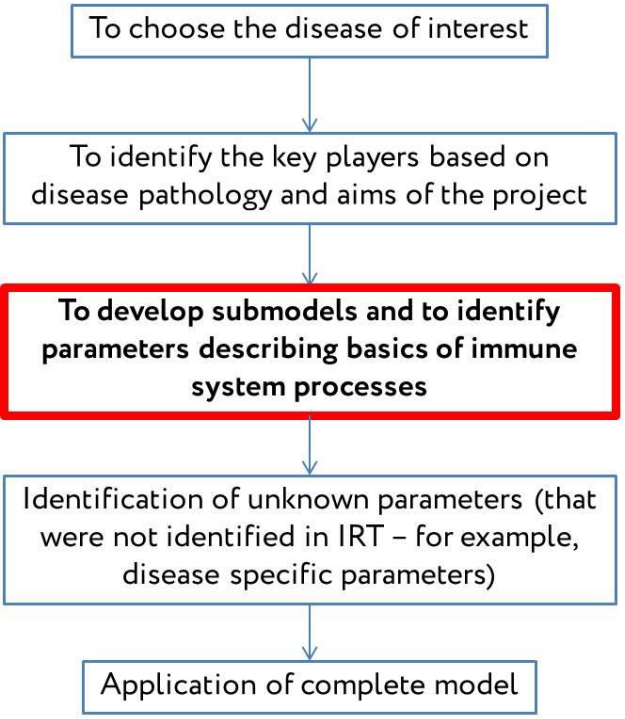
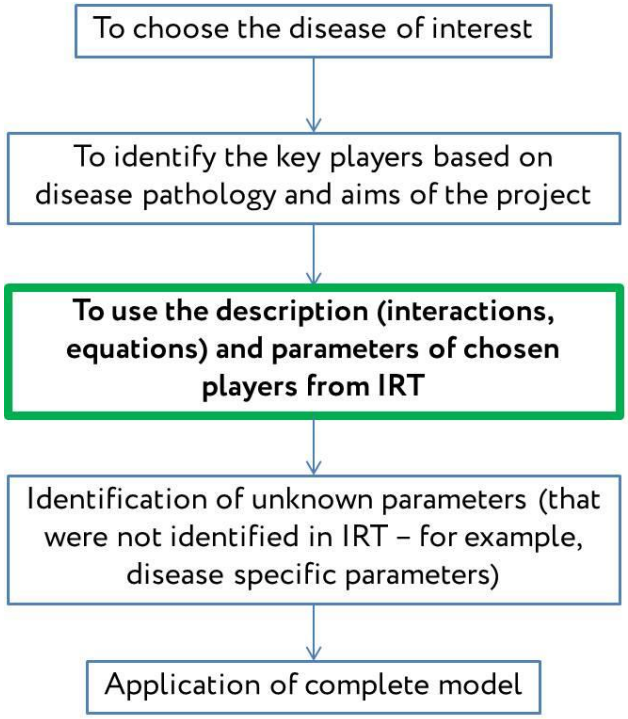
The way how to apply IRT

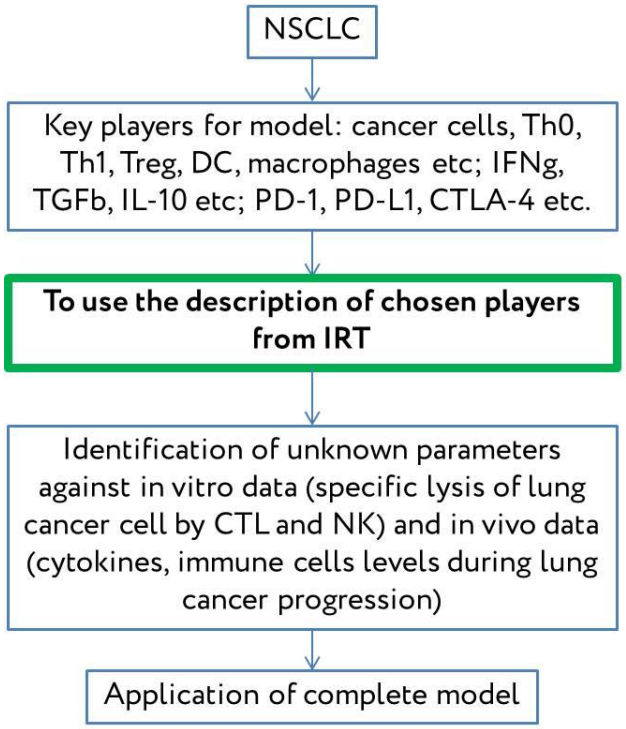
Without IRT



With IRT



Example:
To develop QSP model of NSCLC to optimize treatment with different immuno-oncology compounds (PD-1/PDL1 inhibitors etc).



Conclusion: IRT allows to reduce QSP project duration by weeks or months.

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Demo version

The demo version of IRT database 1.0 is available.

Demo includes:

- IRT navigator 1.0 with complete functionality;
- IRT database 1.0 limited to:
  - Th2 cells passport;
  - IL-4 sources profile;
  - IL-5 sources profile;

To get demo version of IRT database 1.0 please send your request to irt@insysbio.ru.