

Development of Immune Response Template for Systems Pharmacology Modeling of Immunotherapy in Oncology

Evgeny Metelkin, Antonina Nikitich, Oleg Demin Jr, Oleg Demin

Institute for Systems Biology, Moscow, Russia

INTRODUCTION

Immunotherapy is a new class of cancer treatment that works by activation of immune response of patient to fight with tumor cells. The immunotherapy is able to demonstrate very high efficacy in cancer treatment (for, example, PD-1 and PD-L1 inhibitors) the strong stimulation of immune systems could lead to the side effect related to the autoimmunity. That is why optimization of different types of immunotherapies and their combinations is very important to stimulate immune system strong enough to kill tumor cells, but not so strong to cause autoimmunity. The main challenge in optimization of immunotherapies is the complexity of immune system, interactions between different types of immune cells, cancer cells, cytokines, chemokines and other participant of immune response.

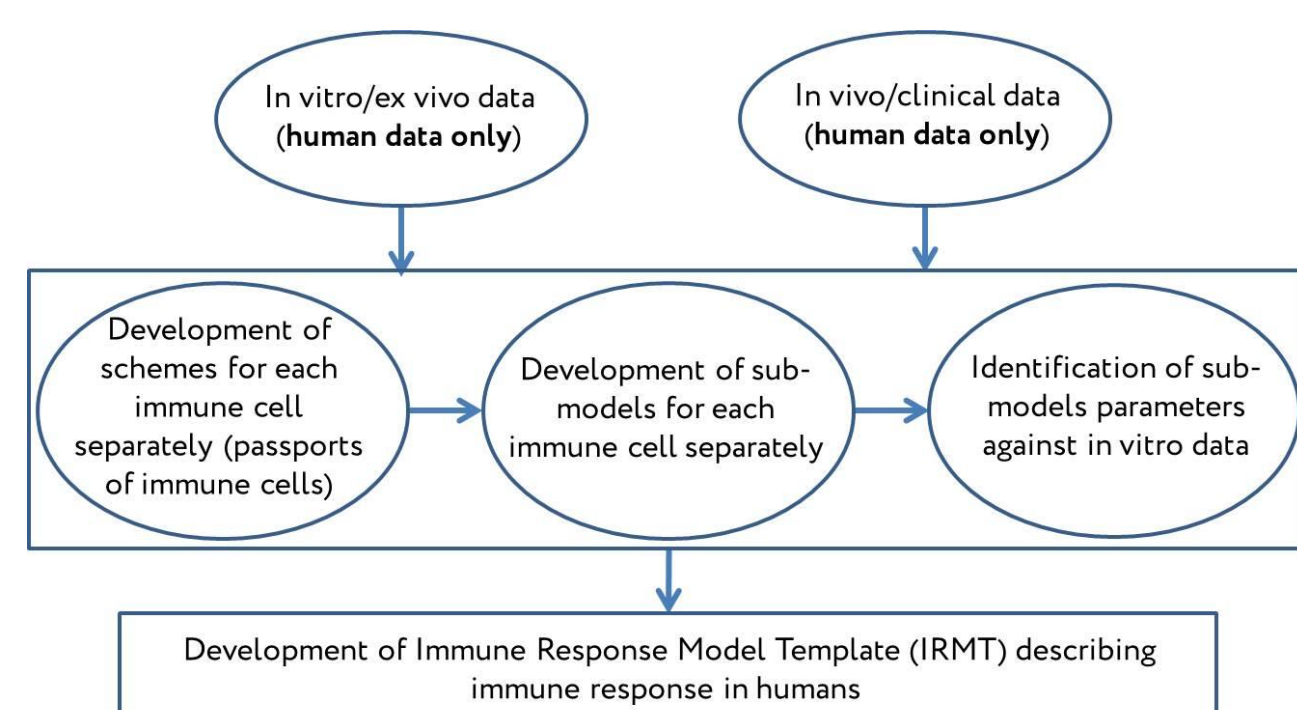
The aim of this study is to develop a tool describing interaction of different types of immune cells, cytokines, chemokines and other participants of immune response.

IRT DESCRIPTION

Immune Response Template (IRT™) is a database for development of QSP platforms/models of different diseases associated with immune response in human.

IRT is a full cycle infrastructure for population, validation and visualization of the available data on immune cells and cytokine interactions in humans. The unique feature of the database is its **focus on tools and support for QSP modeling** by providing

- interactive schemes (passports of immune cells) and tables 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 sub-models to human in vitro and in vivo data;
- extended annotation of rate equations and parameters;
- automatic generation of model templates.



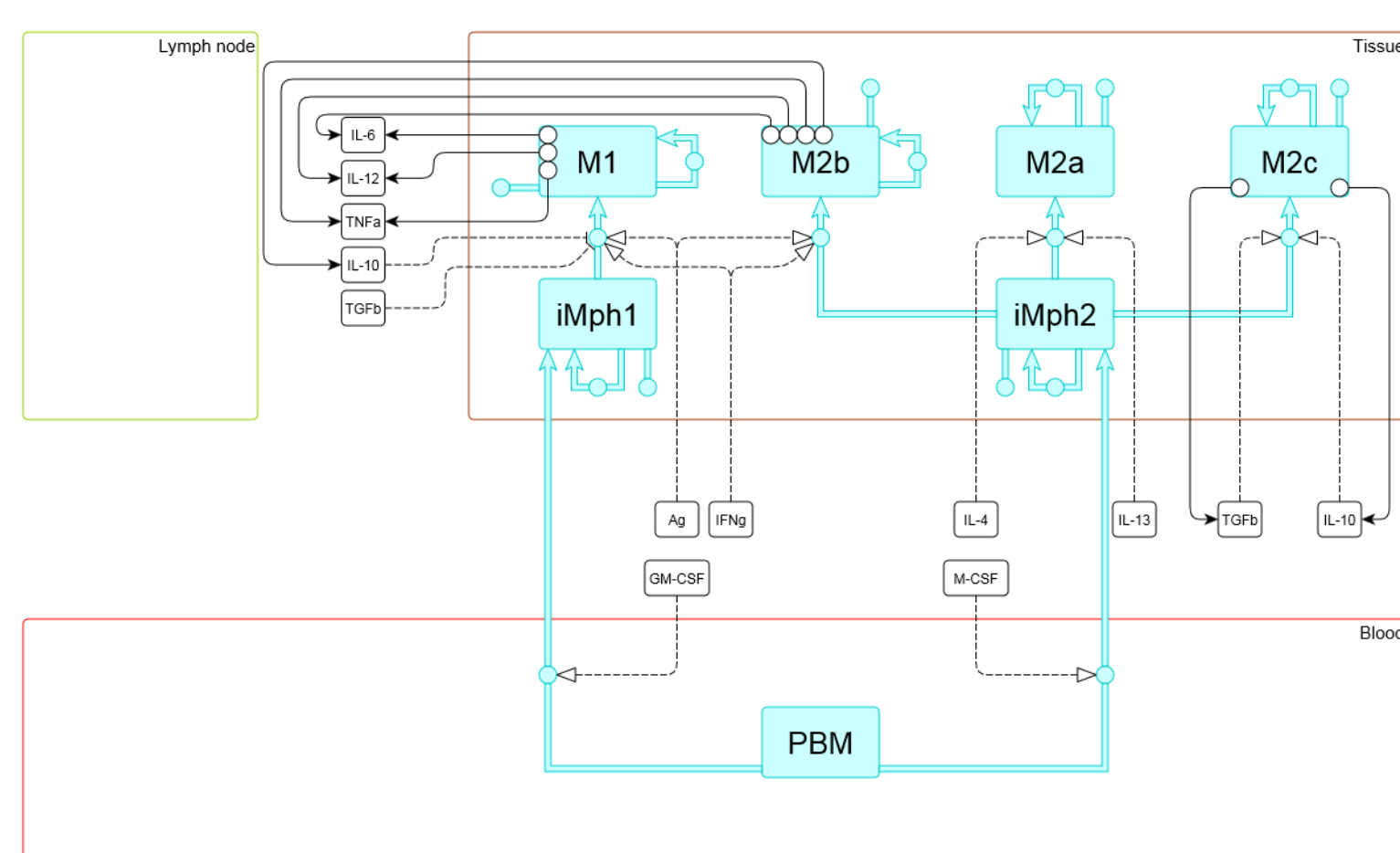
IRT navigator is a tool to access IRT database. IRT navigator provides the intuitive interface for searching the information and model template creation. IRT navigator allows:

- visualization of cell dynamics of immune cells
- navigation across multiple interactions of immune cells
- automatic generation of model template based on the user selection which can be downloaded as SBML file
- automatic summary report generation based on the user selection

IRT CONTENT: IMMUNE CELLS PASSPORTS

For each type of immune cells we have developed “passport” - scheme visualizing literature available experimental facts on

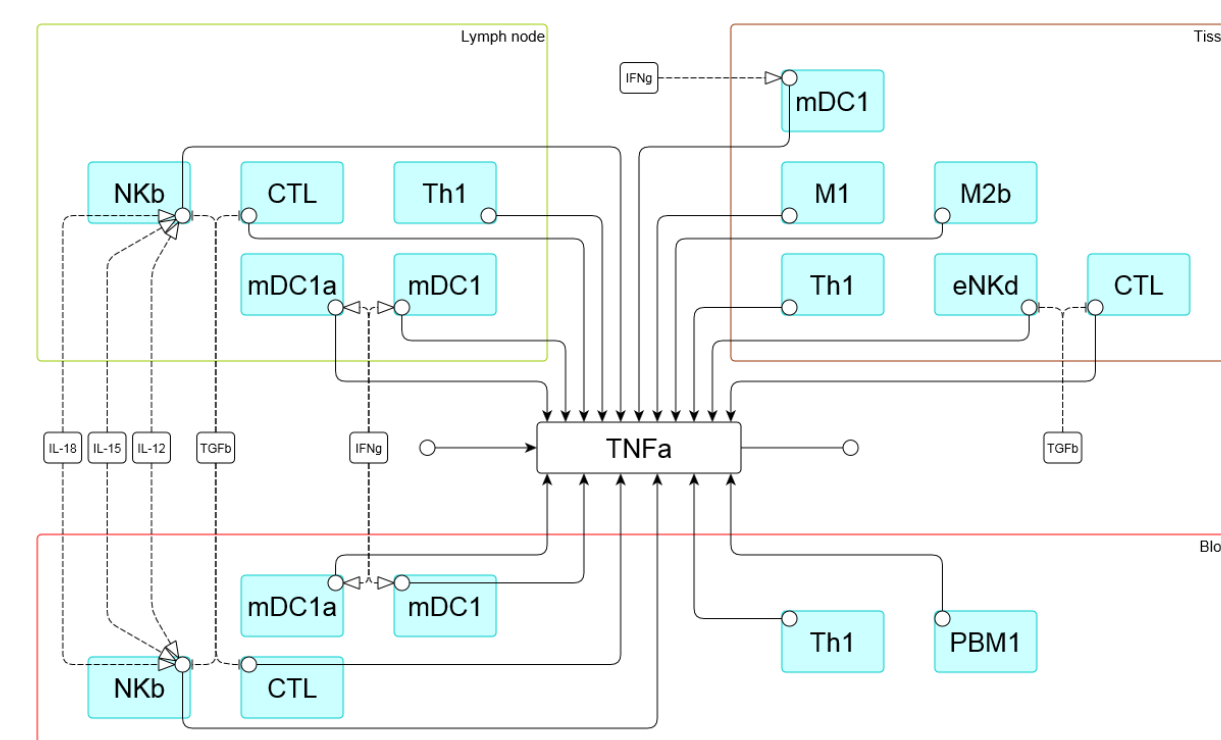
- activation/differentiation and proliferation of the cell;
- cytokines which is synthesized by this type of cell upon activation;
- cytokines/cells that affect this type of cell.



IRT CONTENT: CYTOKINE SOURCES PROFILE

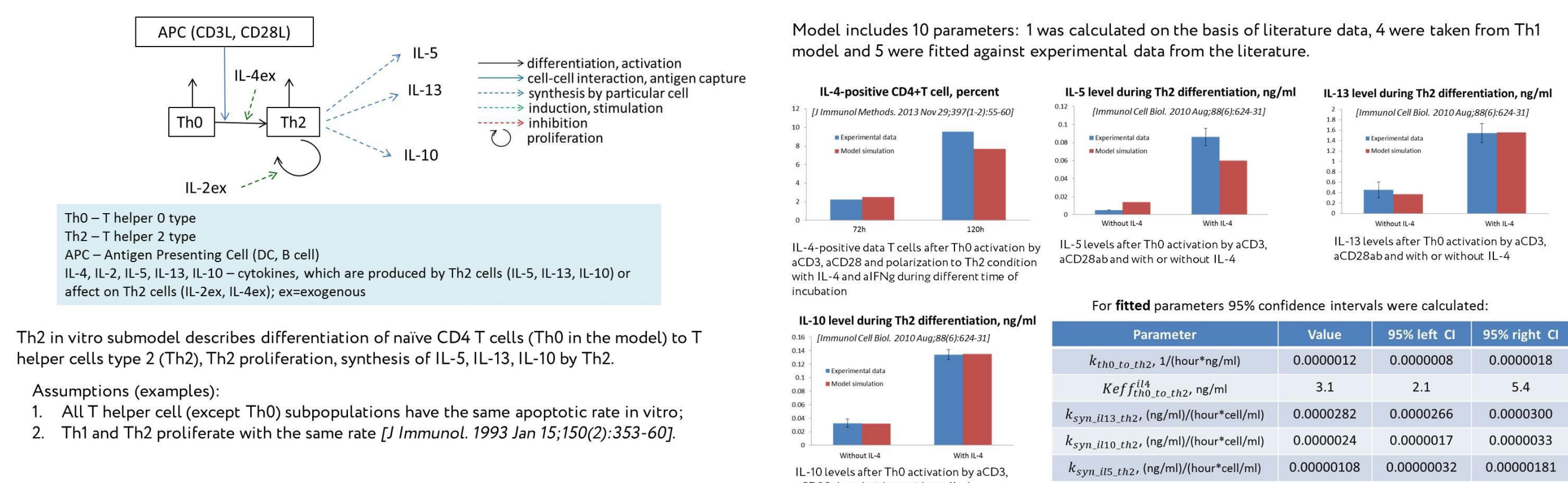
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IRT CONTENT: IMMUNE CELLS SUBMODELS

Submodels describing in vitro cell differentiation, proliferation, cytokines production and their effects were developed and verified for each type of immune cells.



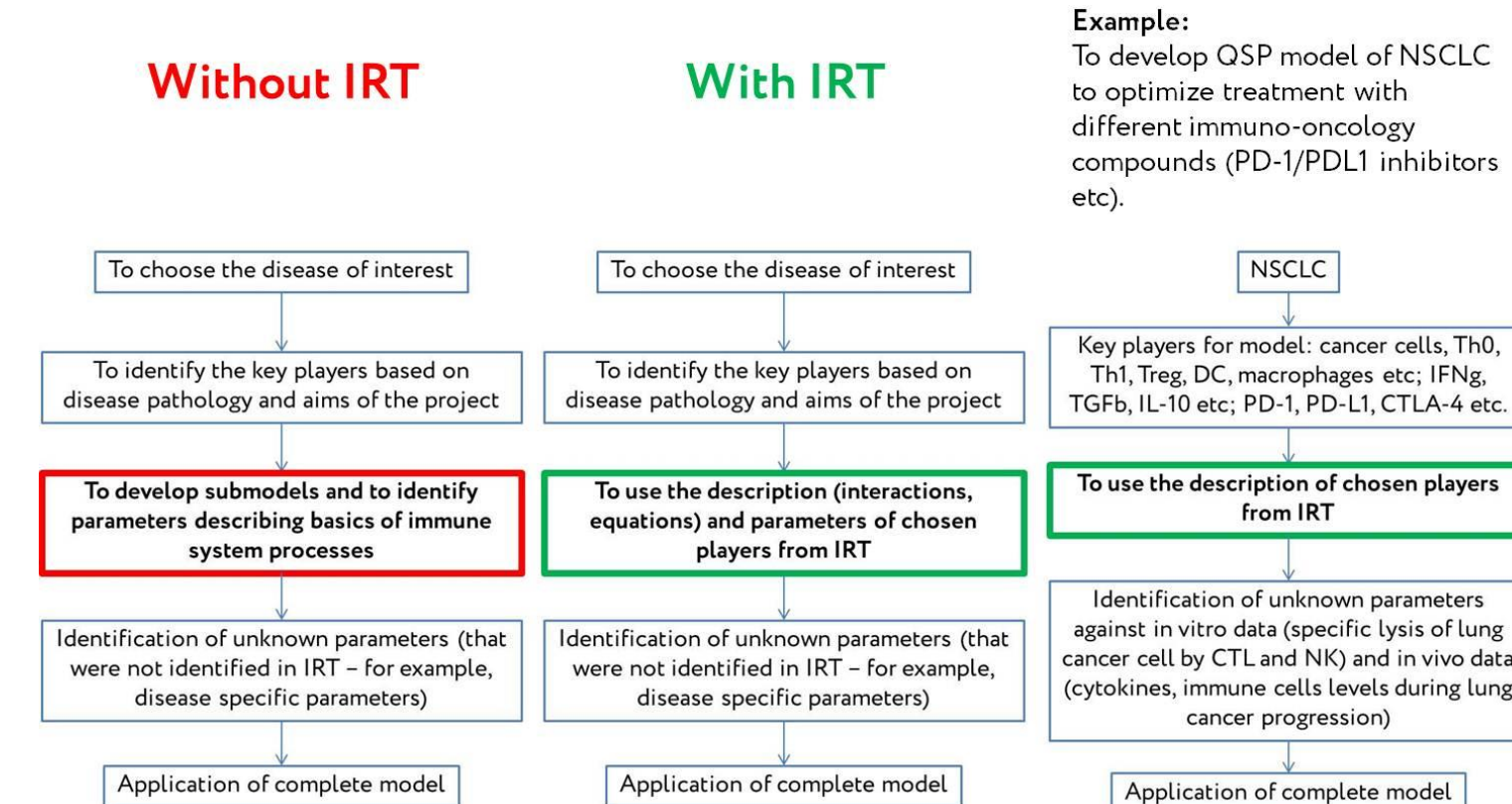
IRT CONTENT: IMMUNE RESPONSE MODEL TEMPLATE

Immune Response Template describes the immune response in human subjects including main immune processes as activation, differentiation, proliferation, apoptosis of immune cells, cytokines synthesis, degradation and their effect, migration of cells. IRT is based on submodels for different immune cells.

Part of parameters for IRT is taken from submodels. Part of parameters were taken from or calculated on the basis of available literature. Other parameters are unknown and free. IRT could be used as a basis for systems pharmacology model describing immune response in human subjects in framework of different diseases like cancer, autoimmune disorders etc.

Immune cells	Cytokines		Surface molecules	Compartments (organs)
NK	GM-CSF	IL-13	CD3	Blood
DC	M-CSF	IL-2	CD28	Lymph Nodes [LN]
Macrophages	IFNγ	IL-21	CD40	Tissue
Monocytes	IL-12	IL-5	PD-1	-
MDSC	IL-6	IL-17 (A,F)	PD-L1	-
B cells	TNFα	IL-23	CTLA-4	-
Naïve CD4 T cells	IL-10	IL-15	MHC-I	-
Th1, Th2, Th17, Treg	TGFβ	IL-18	MHC-II	-
CD8 T cells/CTL	IL-4	IL-1b	CD80/86	-

THE WAY HOW TO APPLY IRT



CONCLUSIONS

IRT recapitulates essential immune response pathways, effect of immune response on tumor and vice versa. IRT will serve as a framework to facilitate understanding of mechanisms of action of different immunotherapies and their effects, predictive biomarkers identification, optimization of regimens and therapies combination, evaluation of new targets and stratification of subjects enrolled in clinical trials.

CONTACTS

For more information, please visit our web site at www.insysbio.ru. IRT development team by e-mail: irt@insysbio.ru.