



# MATHEMATICAL MODELING OF CAR-T IMMUNOTHERAPY IN MULTIPLE MYELOMA

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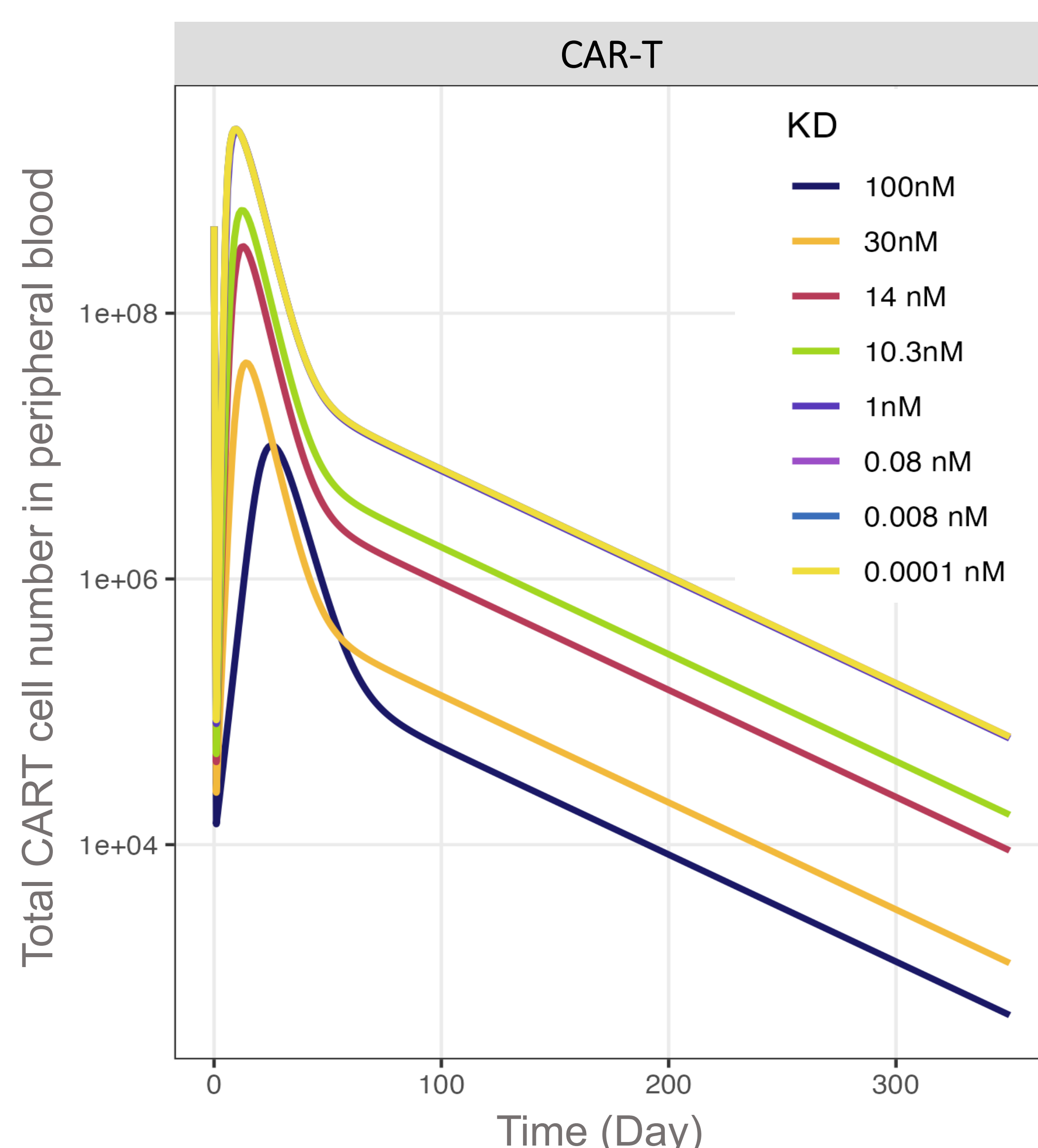
Despite the high efficacy of CAR-T immunotherapy in the treatment of patients with multiple myeloma, the duration of response remains a therapeutic challenge. Efforts are underway to increase CAR-T cell persistence to improve treatment outcomes.

We found clinical trial results with 15 CAR-T cell designs that differed in affinity and avidity binding. Mathematical modelling of CAR-T immunotherapy in multiple myeloma was performed to compare the efficacy of the developed CAR designs. A systematic review of mathematical models was conducted to select a base model, and in vitro data from 17 studies and clinical data from 26 studies were obtained for subsequent modelling.

This study integrates key drug-specific and system-specific parameters responsible for CAR-T cell functionality in preclinical and clinical studies. Using a mathematical model, we were able to characterize (i) the destruction of multiple myeloma tumor cells by CAR-T cells in 13 cell lines with effector to target cell ratios ranging from 1:256 to 80:1, (ii) the multiphase profile of CAR-T cell pharmacokinetics including distribution, expansion, contraction and persistence phases, and (iii) the dynamics of clinical biomarkers in multiple myeloma patients.

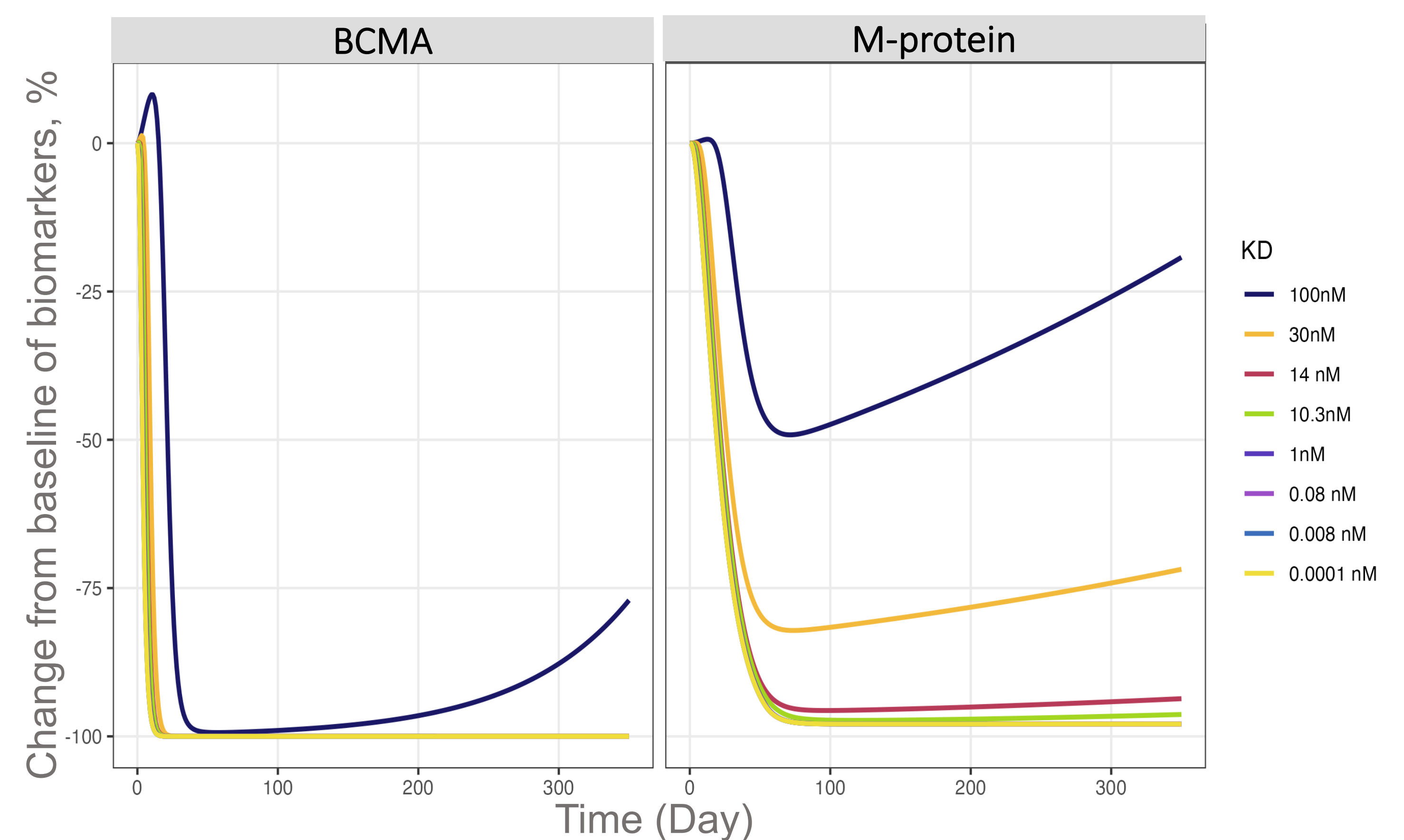
In addition, we compared the efficacy of CAR-T designs with different binding affinity and avidity. It is shown that the lower the value of the dissociation constant, the higher the expansion and persistence of CAR-T cells in the blood (Figure 1).

Figure 1. Predicted CAR-T cell count time profiles for constructs with different dissociation constant values



BCMA and M-protein biomarker value decreases by 100% of the initial level at a value of 14 nanomoles or less (Figure 2).

Figure 2. Predicted time profiles of BCMA and M-protein biomarkers for constructs with different dissociation constant values



It is also shown that constructs that bind two epitopes of BCMA antigen have longer persistence (Figure 3). But with the observed values of dissociation constant and other parameters on biomarker profiles, no effect of changing the number of epitopes was found (Figure 4).

Figure 3. Predicted CAR-T cell count time profiles for constructs with different epitope count values

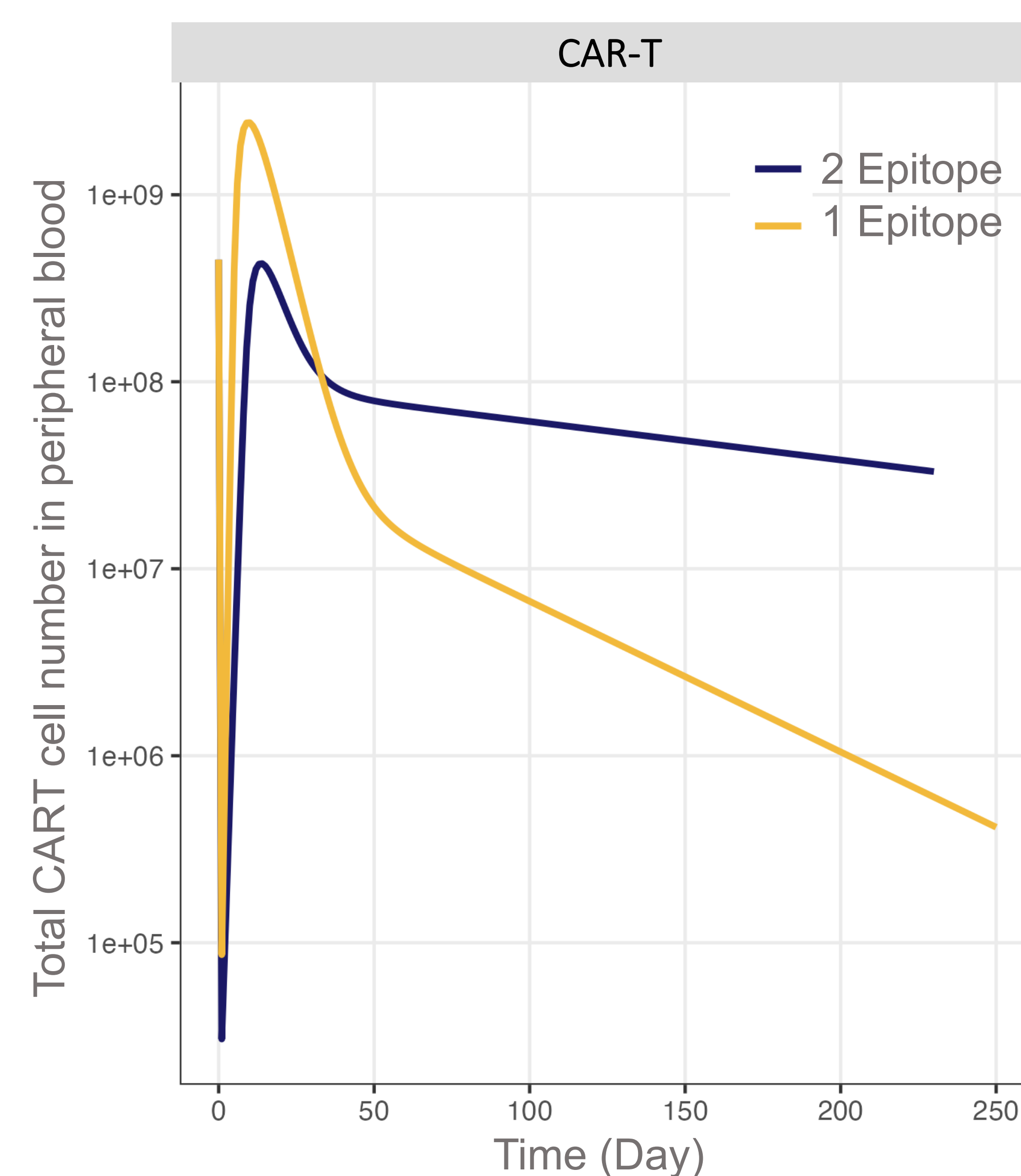
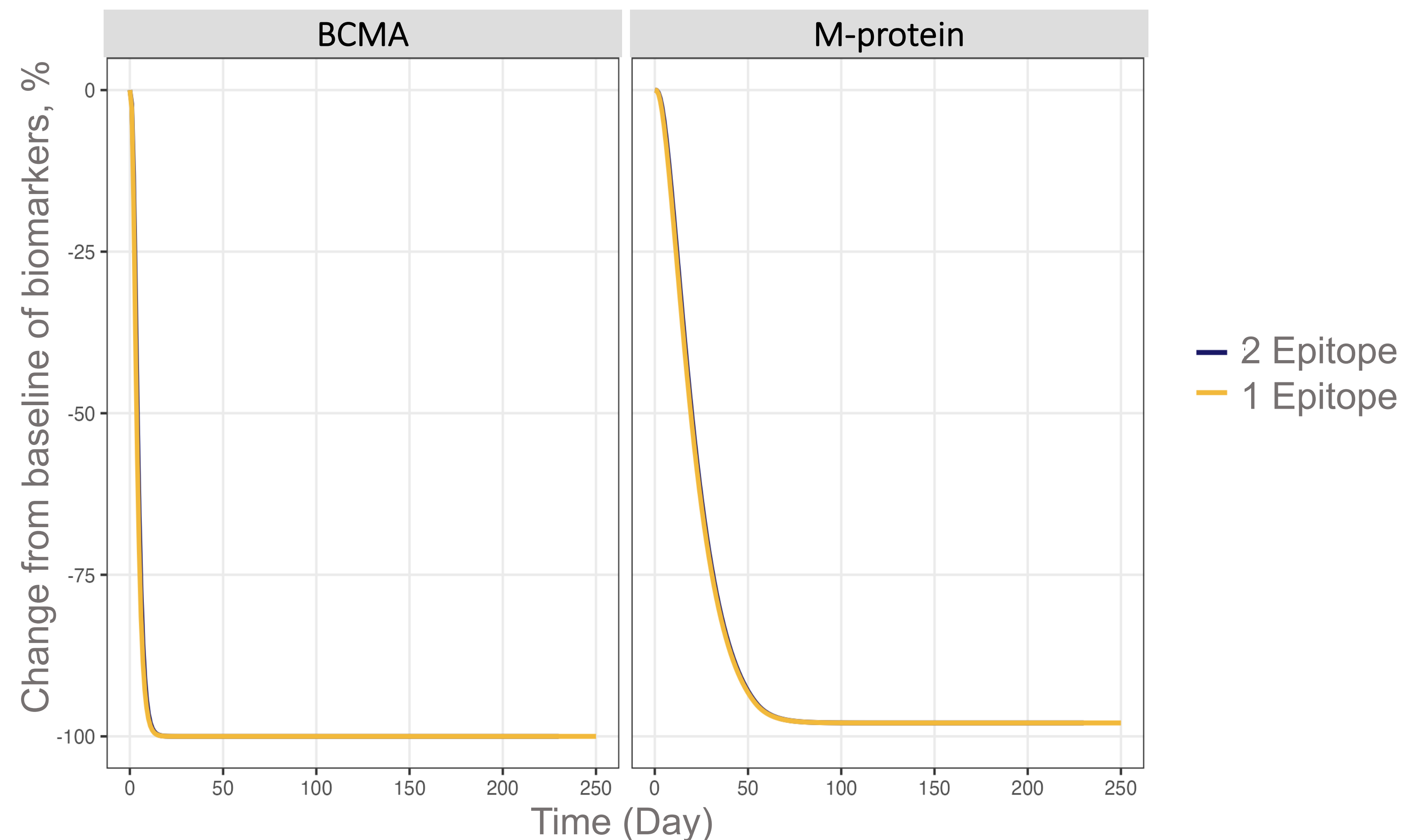


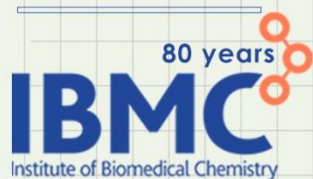
Figure 4. Predicted time profiles of BCMA and M-protein biomarkers for constructs with different epitope counts





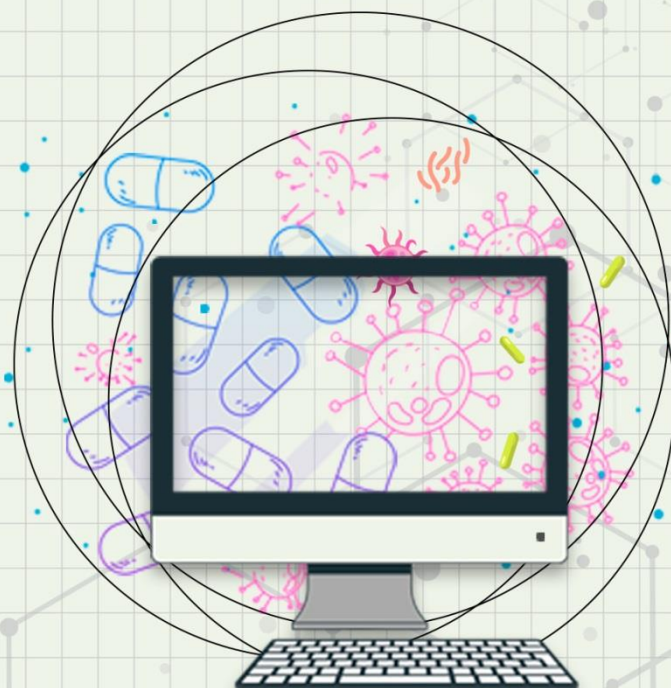


*Russian Academy  
of Sciences*



# **XXX Symposium on Bioinformatics and Computer-Aided Drug Discovery**

## PROCEEDINGS BOOK



**Institute of Biomedical Chemistry**  
Moscow, Russia (Virtual), September 16-18 2024

**Russian Academy of Sciences  
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PROCEEDINGS BOOK OF THE XXX SYMPOSIUM  
“BIOINFORMATICS AND COMPUTER-AIDED DRUG  
DISCOVERY” – Moscow: Institute of  
Biomedical Chemistry, 2024

The materials of the XXX International Symposium “Bioinformatics and Computer-Aided Drug Discovery” (Virtual, 16-18 September 2024) are presented. This Symposium is dedicated to the emerging challenges and opportunities for *in silico* drug discovery. Contemporary fields of biomedical science devoted to the analysis of normal and pathological states of the organism and revealing the pathological processes at the cellular and molecular levels are discussed.

The main topics include: development and practical application of computational methods for finding and validation of new pharmacological targets, *in silico* design of potent and safe pharmaceutical agents, optimization of the structure and properties of drug-like compounds, rational approaches to the utilization of pharmacotherapeutic remedies in medical practice.

This information will be useful for researchers whose investigations are dedicated to creating computational methods and their application to drug research and development using bio- and chemoinformatics methods based on post-genomic technologies. It can also be useful for undergraduate, graduate, and postgraduate students specializing in the relevant fields.

Responsible editors: Corr. Member of Rus. Acad. Sci. V.V. Poroikov, Prof. R.G. Efremov



Dear Colleagues,

On behalf of the Organizing Committee and the Administration of the Institute of Biomedical Chemistry, I am very happy to welcome the participants of the XXX Symposium “Bioinformatics and Computer-Aided Drug Discovery”.

Being initiated by my teacher, the Full Member of the Russian Academy of Sciences, Professor Alexander Archakov, the first Symposium hold in the framework of the II Russian National Congress “Man and Drugs” in 1995. Since then, this meeting has been held annually, organized by the Corresponding Member of Russian Academy of Sciences, Professor Vladimir Poroikov, leading Russian scientist in the field of medical bioinformatics and computer-aided drug discovery, jointly with the Full Member of Russian Academy of Sciences, Professor Nikolay Zefirov, and since 2018 - jointly with Professor Roman Efremov.

In 2024 we are celebrating the 300 years of the Russian Academy of Sciences and 80 years of the Institute of Biomedical Chemistry. The XXX Symposium is dedicated to these significant events, which highlights the continuity and importance of the progress of biomedical science in the discovery of new medicines. Analysis of big biomedical data, development of artificial intelligence & machine learning, extension and expansion of new bio- and chemoinformatics methods provide the pre-requisites for better understanding of pathological processes in the organism, and identification of the promising biomarkers and pharmacological targets. Wide application of in silico methods not only saves human efforts, time and money spent on finding of new more safety and potent drugs, but provides the strong basis for integration of information and extraction of new knowledge in this multidisciplinary area.

In 2023, previous XXIX Symposium attracts more than 400 participants including 46 speakers from Belarus, Brazil, Georgia, Germany, India, Indonesia, Ireland, Israel, Japan, Mexico, The Netherlands, Pakistan, Philippines, Russia, Sweden and USA. Almost seventy young researchers took part in the Young Scientists Contest, and the best reports were awarded by the special Diplomas.

This year more than 450 researchers from 50 countries have been registered to take part in the Symposium. To extend the communication between the participants, the Organizing Committee arranged a distributed in time E-Poster Session that is going during not traditional two-three hours but for 18 days, which helps to overcome the limitations of stirring life of the most people working in science and the time difference for the participants from different continents.

The Symposium allows researchers from many countries to exchange by novel ideas and to discuss the main challenges and opportunities in the field of bioinformatics, chemoinformatics, medicinal chemistry and pharmacology, as well as to find new partners for future collaborative projects.

The main topics of the Symposium are especially important due to the active involvement of our Institute in the project “Digital Biodesign and Personalized Health Care”. This is a global project on the digitalization of health monitoring and healthcare management. As part of this project, Institute of Biomedical Chemistry

developing a digital information platform designed to optimize treatment using modern pharmacotherapy and taking into account the individual peculiarities of the patient.

Supporting and developing traditions of this Symposium, we will make the better future together. I would like to thank all the participants of the Symposium and wish you to get a new knowledge due to the nice lectures, to have very fruitful discussions and to find new friends and partners in collaborative projects for a mutual benefit!

Director of the Institute of Biomedical Chemistry,  
Doctor of Biological Sciences



Elena Ponomarenko





*Dear Colleagues!*

We are pleased to welcome you as participants of the, Jubilee, XXX Symposium “Bioinformatics and Computer-Aided Drug Discovery” (BCADD-2024).

Our Symposia are dedicated to the emerging challenges and opportunities in computer-aided drug discovery. This series of annual Symposia started in 1995 in the framework of the Second Russian National Congress “Man and Drugs”. Originally, it was initiated by the Full Member of the Russian Academy of Sciences Alexander Archakov and co-chaired by Prof. Vladimir Poroikov. An essential contribution to the organization of the first Symposia was made by Professor Alexis Ivanov. In 1996-2017 the Symposia were co-chaired by the Full Member of the Russian Academy of Sciences Nikolay Zefirov and Prof. Vladimir Poroikov. Significant impact on the next Symposia have been provided by Professor Oleg Raevsky, who has initiated the organization of the Russian Section of the International QSAR Society.

At the BCADD-2024 Symposium two invited lectures will be presented, to remind great achievements of Full Member of the Russian Academy of Sciences Nikolay Zefirov and Professor Oleg Raevsky.

Since 2018 the mutual efforts to organize and perform the Symposia are applied by Prof. Vladimir Poroikov and Prof. Roman Efremov.

Many world-wide famous researchers presented their lectures at the past symposia including Per Artursson (Uppsala University, Sweden), Igor Baskin (Lomonosov Moscow State University, Russia), Artem Cherkasov (University of British Columbia, Canada), Alexey Egorov (Lomonosov Moscow State University, Russia), Frank Eisenhaber (A\*STAR Bioinformatics Institute, Singapore), Alexey Finkelstein (Institute of Protein Research, Russia), Viktor Finn (VINITI, Russia), Alexander Gabibov (Institute of Bioorganic Chemistry, Russia), Mikhail Gelfand (Institute for Information Transmission Problems, Russia), Jerome Golebiowski (CNRS GDR “Odorant Odor Olfaction”, France), Viktor Kuzmin (Bogatsky Physico-Chemical Institute, Ukraine), José Medina-Franco (National Autonomous University of Mexico, Mexico), Alexander Nemukhin (Lomonosov Moscow State University, Russia), Kyoung Tai No (Yonsei University, Republic of Korea), Oleg Raevsky (Institute of Physiologically Active Compounds, Russia), Narahari G. Sastry (CSIR-North East Institute of Science and Technology, India), Hanoch Senderowitz (Bar-Ilan University, Israel), Oliver Steck and Andreas Vitte (Tripos, Germany), Igor Tetko (Institute of Structural Biology, Helmholtz Zentrum München, Germany), Vladimir Tumanyan (Institute of Molecular Biology, Russia), Alexandre Varnek (University of Strasbourg, France), Gennady Verkhivker (Chapman University, Irvine, USA), Erik Weber (Environmental Protection Agency, USA), and others.

At the upcoming, XXX Symposium, plenary/keynote lectures and oral talks will be presented by the experienced as well as younger scientists from many countries including Armenia, Australia, China, Germany, Hungary, India, Israel, Mexico, Peru, Russia, Sweden Taiwan, United States and others. Their lectures cover the wide topics dedicated to the development and application of in silico methods for drug



discovery & development. Besides the COVID-19 pandemics is over now, some lessons from *in silico* studies on SARS-CoV-2/COVID-19 will be presented in several talks, which will be useful to combat new biogenic threats in the future.

It is necessary to emphasize that the traditional Young Scientists Contest (YSC) aroused great interest: 41 abstracts by undergraduates and graduates, as well as researchers without scientific degrees under the age of 30 were submitted for participation in the competition. The YSC abstracts were evaluated by seventeen Members of the International Scientific Committee (ISC) including distinguished scientists from Brazil, China, Germany, Greece, India, Israel, Mexico, Russia. Based on the voting of the ISC members and taking into account the geographical diversity of the participants, 18 abstracts have been selected for the flash presentations. The best presentations will be awarded by the Diploma of the First, Second and Third Degrees.

To extend the communication between the participants, the Organizing Committee arranged a distributed in time E-Poster Session that is going during not traditional two-three hours but for 18 days, which helps to overcome the limitations of stirring life of the most people working in science and the time difference for the participants from different continents. The best posters will be awarded by special Diploma.

***The Symposium on Bioinformatics and Computer-Aided Drug Discovery are arranged by scientists for scientists; neither commercial entity is involved in preparing the meeting nor registration fee is requested.***

Let us use the Symposium discussion platform to exchange original scientific ideas, attractive methodological solutions, and breakthrough multidisciplinary technologies. This is especially important in connection with the current situation in the world, which complicate international scientific and educational relationships, efficient exchange of information and data. These factors have always been at the heart of scientific creativity, especially in the field of biomedical research.

We believe that holding our Symposium in the current conditions, involving the participation of scientists from many countries, will help to develop scientific diplomacy, preserve and increase professional and human relations of colleagues, establish new creative connections, and, as a result, increase the efficiency of computer technologies for the discovery of new medicines. We hope that our Symposium will also contribute to reducing tension in the world. The online format provides unique opportunities for this, including talks given by our authoritative colleagues from all over the world.

Welcome to the sessions of the XXX Symposium on Bioinformatics and Computer-Aided Drug Discovery. We wish you very exciting lectures, fruitful communication and valuable discussions!



**Vladimir Poroikov**

Corresponding Member of the Russian  
Academy of Sciences, Prof. Dr.



**Roman Efremov**

Prof. Dr.

# POSTERS

# MATHEMATICAL MODELING OF CAR-T IMMUNOTHERAPY IN MULTIPLE MYELOMA

***A. Punko<sup>1</sup>, A. Volkova<sup>2</sup>***

*<sup>1</sup>Higher School of Economics, Moscow, Russia*

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