T Cell Engineering For Cancer Immunotherapy

MOSHE JADA

Springer Nature
Epstein Barr virus (EBV) was discovered as the first human tumor virus around 50 years ago. Since its discovery in Burkitt's lymphoma it has been associated with various other malignancies, infectious mononucleosis and even autoimmune diseases. The two book volumes on EBV summarize the first 50 years of research on this tumor virus, starting with historical perspectives on discovery, oncogenicity and immune control, reviewing the role that the virus plays in the various associated diseases and concluding with a discussion on how the immune system keeps persistent EBV infection under control in healthy EBV carriers and can be used to treat EBV associated diseases. The respective 32 chapters are written by international experts from three continents for health care providers, biomedical researchers and patients that are affected by EBV. The assembled knowledge should help to understand EBV associated diseases better and to develop EBV specific vaccination in the near future.

Brain Tumor Immunotherapy Springer
Recent advances in understanding of fundamental immunology have created new insights into the dynamic interactions between tumors and the immune system. This includes new understanding of T- and B-cell interaction, immune inhibitory mechanisms including the biology of T regulatory cells, myeloid suppressor cells, and dendritic cell subsets. Enhanced understanding of mechanisms underlying T-cell anergy such as arginine deprivation, immunosuppressive cytokines, defective innate and interferon response pathways, and NKG2D downregulation have all provided new insight into suppression of anti-tumor immunity and tumor evasion. In addition to emerging understanding of tumor evasion, new immune targets such as CTLA4 blockade, NK stimulatory receptors, manipulation of the antigen processing and presentation, cytokine and costimulatory responses all provide new possibilities for enhancing anti-tumor immunity even in tumors previously felt to be resistant to immune attack. Several of these strategies have already been realized in the clinic. The volume will explore evolving paradigms in antigen presentation, dendritic cell biology, the innate response and immunosuppressive mechanisms, and emerging strategies for manipulation of the immune system for therapeutic benefit that have realized success in neuroblastoma, leukemia, melanoma, lung cancer, and allogeneic transplantation. Early successes as well as failures will be highlighted to provide a snapshot of the state of clinical immunotherapy with an eye to future possibilities such as combination therapies, adoptive T-cell transfer, and the retargeting of immune cells via T-cell receptor engineering.

Immunotherapy of Hepatocellular Carcinoma Academic Press
Normative Biology, Husbandry, and Models, the third volume in the four volume set, The Mouse in Biomedical Research, encompasses 23 chapters whose contents provide a broad overview on the laboratory mouse's normative biology, husbandry, and its use as a model in biomedical research. This consists of chapters on behavior, physiology, reproductive physiology, anatomy, endocrinology, hematology, and clinical chemistry. Other chapters cover management, as well as nutrition, gnotobiotics and disease surveillance. There are also individual chapters describing the mouse as a model for the study of aging, eye research, neurodegenerative diseases, convulsive disorders, diabetes, and cardiovascular and skin diseases. Chapters on imaging techniques and the use of the mouse in assays of biological products are also included.

Systemic Drug Delivery Strategies Springer
This book covers multi-scale biomechanics for oncology, ranging from cells and tissues to whole organ. Topics covered include, but not limited to, biomaterials in mechano-oncology, non-invasive imaging techniques, mechanical models of cell migration, cancer cell mechanics, and platelet-based drug delivery for cancer applications. This is an ideal book for graduate students, biomedical engineers, and researchers in the field of mechanobiology and oncology. This book also: Describes how mechanical properties of cancer cells, the extracellular matrix, tumor microenvironment and immuno-editing, and fluid flow dynamics contribute to tumor progression and the metastatic process Provides the latest research on non-invasive imaging, including traction force microscopy and brillouin confocal microscopy Includes insight into NCIs' role in supporting biomechanics in oncology research Details how biomaterials in mechano-oncology can be used as a means to tune materials to study cancer

Developments in T Cell Based Cancer Immunotherapies Springer
Cancer immunotherapy has become the new medicine for cancer patients providing curative hopes. The adoptive cell transfer of engineered T cells has demonstrated promising clinical response rates, especially for chimeric antigen receptor (CAR) therapies and T cell receptor (TCR) engineered therapies. This dissertation aims to extend the findings of previous engineered T cell therapies focusing on TCR-engineered T cells. Two TCRs are studied here: NY-ESO-1-specific TCR (esoTCR) and invariant natural killer T (iNKT) cell TCR. Towards the "off-the-shelf" T cell immunotherapy, we demonstrated the efforts in developing the TCR toolbox, the ex vivo allogeneic T cell generation platform, combination engineering methods for next-generation allogeneic T cell product, and nanomaterials for T cell activation and expansion. NY-ESO-1 attracts wide attention for developing targeted cancer therapies for its broad aberrant expression across tumor types and strong ability to elicit immune responses. Due to the MHC restriction nature of TCR, a toolbox of esoTCRs with various NY-ESO-1 epitope specificity and MHC restriction is in great need to expand the patient pool and prevent tumor evasion through the loss of MHC heterozygosity. Chapter 2 of this dissertation will present the work on isolation and characterization of NY-ESO-1-specific TCRs restricted on various MHCs. Most current engineered T cell therapies, including CAR and TCR therapies, fall under autologous cell therapy. The autologous approach has demonstrated its feasibility and effectiveness. The personalized nature of autologous therapies has also greatly limited the further extended use of engineered T cells in the clinic. In Chapters 3 and 4, we established a novel ex vivo HSC-based TCR-engineered T cell generation platform for allogeneic "off-the-shelf" T cell therapies for cancer. In two separate works, we demonstrated the use of esoTCR and iNKT TCR in this platform. The combinational uses of CAR, CRISPR-Cas9 gene editing, and other enhancement genes were also explored in these two chapters. T cell activation and expansion is an essential step required for all T cell-based immunotherapies. The developmental path of T cell activating methods starts from the simple addition of anti-CD3 antibodies to magnetic antibody-conjugated beads that are commercially available nowadays. Striving to mimic the natural cell-cell interaction and immunological synapse relating to T cell activation, in Chapter 5, we present a novel nanomaterial-based method for ultrahigh T cell activation and expansion. Collectively, the work described here advances the field of T cell therapies by enriching the toolbox of TCRs restricted on various MHC, establishing an ex vivo HSC-based TCR-engineered T cell generation platform which provides new allogeneic T cell sources towards the "off-the-shelf" T cell therapies for cancer patients, and providing a new nanomaterial-based method for ultrahigh T cell activation and expansion.

Synthetic Biology Elsevier Inc. Chapters
Immunotherapy is a form of cancer therapy that harnesses the body's immune system to destroy cancer cells. In recent years, immunotherapies have been developed for several cancers, including advanced melanoma, lung cancer, and kidney cancer. In some patients with metastatic cancers who have not responded well to other treatments, immunotherapy treatment has resulted in complete and durable responses. Given these promising findings, it is hoped that continued immunotherapy research and development will produce better cancer treatments that improve patient outcomes. With this promise, however, there is also recognition that the clinical and biological landscape for immunotherapies is novel and not yet well understood. For example, adverse events with immunotherapy treatment are

quite different from those experienced with other types of cancer therapy. Similarly, immunotherapy dosing, therapeutic responses, and response time lines are also markedly different from other cancer therapies. To examine these challenges and explore strategies to overcome them, the National Academies of Sciences, Engineering, and Medicine held a workshop in February and March of 2016. This report summarizes the presentations and discussions from the workshop.

Biomechanics in Oncology Springer

The study of carbonic anhydrase has spanned multiple generations of scientists. Carbonic anhydrase was first discovered in 1932 by Meldrum and Roughton. Inhibition by sulfanilamide was shown in 1940 by Mann and Keilin. Even Hans Krebs contributed to early studies with a paper in 1948 showing the relationship of 25 different sulfonamides to CA inhibition. It was he who pointed out the importance of both the charged and uncharged character of these compounds for physiological experiments. The field of study that focuses on carbonic anhydrase (CA) has exploded in recent years with the identification of new families and isoforms. The CAs are metalloenzymes which are comprised of 5 structurally different families: the alpha, beta, gamma, and delta, and epsilon classes. The alpha class is found primarily in animals with several isoforms associated with human disease. The beta CAs are expressed primarily in plants and are the most divergent. The gamma CAs are the most ancient. These are structurally related to the beta CAs, but have a mechanism more similar to the alpha CAs. The delta CAs are found in marine algae and diflagellates. The epsilon class is found in prokaryotes in which it is part of the carboxysome shell perhaps supplying RuBisCO with CO2 for carbon fixation. With the excitement surrounding the discovery of disease-related CAs, scientists have redoubled their efforts to better understand structure-function relationships, to design high affinity, isotype-specific inhibitors, and to delineate signaling systems that play regulatory roles over expression and activity. We have designed the book to cover basic information of mechanism, structure, and function of the CA families. The authors included in this book bring to light the newest data with regard to the role of CA in physiology and pathology, across phylums, and in unique environmental niches.

The Heterogeneity of Cancer Metabolism Springer Science & Business Media

This volume illustrates the salient aspects of cancer biology relevant to the successful implementation of immunotherapy. Topics include enhancement of antigen-specific immune responses by anti-cancer vaccines, modulation of the function of T cells within the tumor microenvironment, and the effects of genetic, epigenetic, developmental, and environmental determinants on T cell function. Other topics covered include the ex vivo expansion of T or other immune cells and their genetic modification or reprogramming to increase their ability to survive and expand when adoptively transferred back to the patients. Specific attention is devoted to the genetic manipulation of T cells through the introduction of re-directed T cell receptors, chimeric antibody receptors, and other genetic manipulation aimed at improving their effectiveness as anti-cancer agents. Furthermore, the revolutionary role of checkpoint inhibitors and their potential in combination with other immunotherapeutic approaches or with standard chemo and radiation therapy are extensively discussed.

Genome Engineering to Expand Applications of Human T-cell Immunotherapy Frontiers Media SA

Engineering Technologies and Clinical Translation: Volume 3: Delivery Strategies and Engineering Technologies in Cancer Immunotherapy examines the challenges of delivering immuno-oncology therapies, focusing specifically on the development of solutions for drug delivery and its clinical outcomes. Immuno-oncology (IO) is a growing field of medicine at the interface of immunology and cancer biology leading to development of novel therapeutic approaches, such as chimeric antigen receptor T-cell (CAR-T) and immune checkpoint blockade antibodies, that are clinically approved approaches for cancer therapy. Although currently approved IO approaches have shown tremendous promise for select types of cancers, broad application of IO strategies could even further improve the clinical success, especially for diseases such as pancreatic cancer, brain tumors where the success of IO so far has been limited. This volume of Delivery Strategies and Engineering Technologies in Cancer Immunotherapy discusses biomaterial, microfluidic, and biodegradable devices, engineered microbes, personalized medicine, clinical approval process, and many other IO technologies. Engineering Technologies and Clinical Translation: Volume 3: Delivery Strategies and Engineering Technologies in Cancer Immunotherapy creates a comprehensive treaty that engages the scientific and medical community who are involved in the challenges of immunology, cancer biology, and therapeutics with possible solutions from the nanotechnology and drug delivery side. Explores engineering technologies and their clinical translation in a comprehensive way Presents forecasting on the future of nanotechnology and drug delivery for IO Engages the scientific and medical community who are involved in the challenges of immunology, cancer biology, and therapeutics with possible solutions from the nanotechnology and drug delivery side

Immuno-Oncology Elsevier

In The Ontario Cancer Institute Ernest McCulloch discusses how the institute, dedicated to the goal of reducing the burden of cancer, continuously strove for excellence and shows how both original and collaborative work were encouraged within a supportive environment. To achieve this goal the institute divided its operation into four strands: two of the strands were the research areas – the study of advanced radiation therapy and biology, which worked separatively but cooperatively; a third was patient care; and the fourth element was leadership, provided by the clinical chiefs, the heads of the research divisions, and the administration, in particular the institute's first administrator, John Law. Together these strands helped create a philosophy that made the Ontario Cancer Institute unique and provided the basis for its national and international success. Essential to these successes was a new graduate department, Medical Biophysics, based in the University of Toronto School of Graduate Studies. This department, which provided an innovative, research-based doctoral and masters program, meant that the OCI could accurately be described as a centre for cancer treatment, research, and education. McCulloch describes how the first quantitative assay for stem cells played a major role in bringing OCI research to the international stage as well as influencing other science and much of the clinical thinking in the Institute. Other major advances that brought international recognition have been the identification of the mechanisms that allow cancer cells to resist death from the effects of a variety of different tumours and the isolation of the gene that encodes the T cell receptor, a critical part of the immune apparatus for dealing with foreign cells and viruses. McCulloch also details how lack of space to meet growing demands was a continuing source of frustration and disagreement, and how sometimes serious interpersonal problems hindered the forward thrust of development. Describing these events as well as institute's successes, he provides an insight into the history of Canada's premier cancer research centre.

Engineering T Cells to Improve the Efficacy and Safety of Adoptive T-cell Therapy Academic Press

Systemic Drug Delivery Strategies: Delivery Strategies and Engineering Technologies in Cancer Immunotherapy, Volume 2 examines the challenges of delivering immuno-oncology therapies, focusing specifically on the multiple technologies of affective drug delivery strategies. Immuno-oncology (IO) is a growing field of medicine at the interface of immunology and cancer biology leading to development of novel therapeutic approaches, such as chimeric antigen receptor T-cell (CAR-T) and immune checkpoint blockade antibodies, that are clinically approved approaches for cancer therapy. Although currently approved IO approaches have shown tremendous promise for select types of cancers, broad application of IO strategies could even further improve the clinical success, especially for diseases such as pancreatic cancer, brain tumors where the success of IO so far has been limited. This volume of Delivery Strategies and Engineering Technologies in Cancer Immunotherapy discusses methods of targeting tumors, CRISPR technology, and vaccine delivery among many other delivery strategies. Systemic Drug Delivery Strategies: Delivery Strategies and Engineering Technologies in Cancer Immunotherapy, Volume 2 creates a comprehensive treaty that engages the scientific and medical community who are involved in the challenges of immunology, cancer biology, and therapeutics with possible solutions from the nanotechnology and drug delivery side. Comprehensive treaty covering all aspects of immuno-oncology (IO) Novel strategies for delivery of IO therapeutics and vaccines Forecasting on the future of nanotechnology and drug delivery for IO

Policy Issues in the Clinical Development and Use of Immunotherapy for Cancer Treatment Karger Medical and Scientific Publishers

Delivery Technologies for Immuno-Oncology: Volume 1: Delivery Strategies and Engineering Technologies in Cancer Immunotherapy examines the challenges of delivering immuno-oncology therapies. Immuno-oncology (IO) is a growing field of medicine at the interface of immunology and cancer biology leading to development of novel therapeutic approaches, such as chimeric antigen receptor T-cell (CAR-T) and immune checkpoint blockade antibodies, that are clinically approved approaches for cancer therapy. Although currently approved IO approaches have shown tremendous promise for select types of cancers, broad application of IO strategies could even further improve the clinical success, especially for diseases such as pancreatic cancer, brain tumors where the success of IO so far has been limited. Nanotechnology-based targeted delivery strategies could improve the delivery efficiency of IO agents as well as provide additional avenues for novel therapeutic and vaccination strategies. Additionally, a number of locally-administered immunogenic scaffolds and therapeutic strategies, such as the use of STING agonist, could benefit from rationally designed biomaterials and delivery approaches. Delivery Technologies for Immuno-Oncology: Volume 1: Delivery Strategies and Engineering Technologies in Cancer Immunotherapy creates a comprehensive treaty that engages the scientific and medical community who are involved in the challenges of immunology, cancer biology, and therapeutics with possible solutions from the nanotechnology and drug delivery side. Comprehensive treaty covering all aspects of immuno-oncology (IO) Novel strategies for delivery of IO therapeutics and vaccines Forecasting on the future of nanotechnology and drug delivery for IO

Ontario Cancer Institute John Wiley & Sons

Adoptive cell therapy for cancer using tumor antigen-reactive cytotoxic lymphocytes or with tumor infiltrating lymphocytes has been shown to be a potent therapy for metastatic cancer. The generation of tumor-reactive T cells is not always possible in all of the patients. To overcome this limitation, investigators can now insert highly avid T-cell receptors (TCR) into T cells that can recognize tumor antigens. Genetic engineering of TCR genes into normal T cells is a powerful new strategy to generate large numbers of defined antigen-specific cells for therapeutic application. This approach has evolved beyond experimental stage into a clinical reality. The feasibility of TCR engineered T cells has been shown to be an effective clinical strategy resulting in the regression of established tumors in recent clinical trials. In this chapter, the progress and prospects of TCR engineered T cells as a therapeutic strategy for treating patients with cancer are discussed.

Targeting Cancer Stem Cells by T Cell Engineering Springer Nature

In this book we provide insights into liver – cancer and immunology. Experts in the field provide an overview over fundamental immunological questions in liver cancer and tumorimmunology, which form the base for immune based approaches in HCC, which gain increasing interest in the community due to first promising results obtained in early clinical trials. Hepatocellular carcinoma (HCC) is the third most common cause of cancer related death in the United States. Treatment options are limited. Viral hepatitis is one of the major risk factors for HCC, which represents a typical “inflammation-induced” cancer. Immune-based treatment approaches have revolutionized oncology in recent years. Various treatment strategies have received FDA approval including dendritic cell vaccination, for prostate cancer as well as immune checkpoint inhibition targeting the CTLA4 or the PD1/PDL1 axis in melanoma, lung, and kidney cancer. Additionally, cell based therapies (adoptive T cell therapy, CAR T cells and TCR transduced T cells) have demonstrated significant efficacy in patients with B cell malignancies and melanoma. Immune checkpoint inhibitors in particular have generated enormous excitement across the entire field of oncology, providing a significant benefit to a minority of patients.

γδ T cells in Cancer Chimeric Antigen Receptor T-Cell Therapies for Cancer E-Book

Over the last decade, immuno-oncology has witnessed an astonishing pace of discovery and innovation translating into unprecedented successes in the clinical setting, arguably representing one of the most profound and transforming revolution in the history of cancer therapy. This book provides a concise and accurate outline of the main developments in major tumor types including melanoma, lung, breast, brain and renal cell cancers. In addition, transversal chapters that describe the commonalities of some of the therapeutic strategies are provided to cover topics like immune checkpoint biology, T cell engineering or rational combination therapies. Each chapter has been authored by senior key opinion leaders in their respective fields to provide the most up-to-date view on cancer immuno-oncology. To reflect on the key translational aspect of immuno-oncology, all chapters are making explicit connections between basic science discoveries and the resulting translational therapeutic strategies. Immuno-Oncology will be an invaluable source of information for scientists interested in the translation of basic immunology into the clinical practice, as well as for clinician interested in deepening their knowledge of current and upcoming immune strategies in the fight against cancers.

Cancer Immunology and Immunotherapy Springer Science & Business Media

This open access volume will introduce recent discoveries in cancer metabolism since the publication of the first edition in 2018, providing readers with an up-to-date understanding of developments in the field. Genetic alterations in cancer, in addition to being the fundamental drivers of tumorigenesis, can give rise to a variety of metabolic adaptations that allow cancer cells to survive and proliferate in diverse tumor microenvironments. This metabolic flexibility is different from normal cellular metabolic processes and leads to heterogeneity in cancer metabolism within the same cancer type or even within the same tumor. In this book, the authors delve into the complexity and diversity of cancer metabolism and highlight how understanding the heterogeneity of cancer metabolism is fundamental to the development of effective metabolism-based therapeutic strategies for cancer treatment. Deciphering how cancer cells utilize various nutrient resources will enable clinicians and researchers to pair specific chemotherapeutic agents with patients who are most likely to respond with positive outcomes, allowing for more cost-effective and personalized cancer treatment. This book has four major parts. Part one will cover the basic metabolism of cancer cells, followed by a discussion of the heterogeneity of cancer metabolism in part two. Part three

addresses the relationship between cancer cells and cancer-associated fibroblasts, and the new part four will explore the metabolic interplay between cancer and other diseases. This new section makes the book unique from other texts currently available on the market. The second edition will be useful for cancer metabolism researchers, cancer biologists, epidemiologists, physicians, health care professionals in related disciplines, policymakers, marketing and economic strategists, among others. It may also be used in courses such as intro to cancer metabolism, cancer biology, and related biochemistry courses for undergraduate and graduate students.

Carbonic Anhydrase: Mechanism, Regulation, Links to Disease, and Industrial Applications Frontiers Media SA

We acknowledge the initiation and support of this Research Topic by the International Union of Immunological Societies (IUIS). Dr. Dieter Kabelitz currently serves as the chairman for the IUIS Education Committee. Topic Editor Prof. Ilan Bank is Chief Scientific Officer of GammaCell Bio-Technologies Ltd. Topic Editor Prof. Jurgen Kuball is co-founder and scientific advisor of GADETA. Topic Editor Prof. Bruno Silva-Santos is co-founder of Lymphact S.A., a company now owned by GammaDelta Therapeutics. All other Topic Editors declare no competing interests with regards to the Research Topic subject.

Ex Vivo Cell Therapy John Wiley & Sons

An authoritative panel of researchers and clinicians critically reviews the entire field to provide a comprehensive guide to modern brain tumor immunotherapy and thereby enhance future research in this area. The contributors detail many of the key laboratory experiments and clinical protocols that are currently being investigated, integrate the available information from previous and ongoing research, and help define the current status of the field. Topics range from adoptive cellular and antibody-mediated immunotherapy of brain tumors to tumor vaccines and related strategies, and include many vanguard experimental strategies and immunological techniques for studying brain tumor immunotherapy. Cutting-edge and comprehensive, Brain Tumor Immunotherapy brings together all the important recent advances in our understanding of central nervous system tumor immunology and illustrates in powerful detail the many new applications now harnessing the immune response for brain tumor therapeutics.

Chimeric Antigen Receptor T-Cell Therapies for Cancer E-Book Springer Science & Business Media

Adoptive T-cell therapy, particularly chimeric antigen receptor (CAR) therapy, is a revolutionary and quickly-evolving means of treating cancer patients who can no longer be helped by standard therapies. In multiple clinical trials, including our own at Seattle Children’s Hospital, CD19 CAR therapy for B-cell leukemia and lymphoma has achieved a complete remission rate of >90%. Unfortunately, in its present form, CAR therapy has had limited success against solid tumors. It is also not currently an option for patients who lack sufficient numbers of their own T-cells due to their disease or prior treatments. Thus, genome engineering strategies to overcome these limitations could be of great benefit to patients. We chose a two-pronged approach to achieve this goal: knock-out of the endogenous TCR and multiplex knock-out of the T-cell inhibitory checkpoints PD-1, Tim3, Lag3, and TIGIT. Knocking out these inhibitory checkpoint proteins specifically in the CAR T-cells will maintain the synergistic effects recently seen in combination monoclonal antibody therapy without the serious, sometimes fatal, immune-mediated side effects seen with systemic antibody therapy. To this end, we first developed a linear mRNA expression vector with a long, encoded poly(A) tail to allow transient delivery of nucleases such as TALENs or CRISPR to primary human cells in a consistent, clinically applicable, and scalable fashion. We then used IVT mRNA made from this vector to deliver a TALEN pair targeting the TCR locus to CD19 CAR T-cells, and demonstrated that removal of the endogenous TCR does not hinder CAR T-cell function in vitro or in vivo in a murine xenograft tumor model. Knockout of the endogenous TCR will facilitate production of an allogeneic CAR T-cell product to be used as a bridge to HSCT in patients who cannot receive autologous CAR therapy. Removal of the endogenous TCR will also add a measure of safety when creating CAR T-cells lacking inhibitory checkpoint proteins by preventing GvHD while retaining anti-tumor effects. These technologies and methods may allow a wider variety of patients to benefit from the recent advances in CAR T-cell therapy.

Engineering Technologies and Clinical Translation Frontiers Media SA

Chimeric antigen receptor (CAR) T cells are a promising cancer therapeutic, as they can specifically redirect the cytotoxic function of a T cell to a chosen target of interest. CAR T cells have been successful in clinical trials against hematological cancers, but have experienced low efficacy against solid tumors for a number of reasons, including a paucity of tumor-specific antigens to target and a highly immunosuppressive solid tumor microenvironment. In chapter 2 of this thesis, we develop a strategy to target multiple solid tumor types through markers in their microenvironment. The use of single domain antibody (VHH)-based CAR T cells that recognize these markers circumvents the need for tumor-specific targets. Chapter 3 will describe methods to overcome the immunosuppressive microenvironment of solid tumors. Here, we have developed VHH-secreting CAR T cells that can modulate additional aspects of the tumor microenvironment, including the engagement of the innate immune system through secretion of a VHH against an inhibitor of phagocytosis. We show that this strategy of VHH-secretion by CAR T cells can lead to significant benefits in outcome. We also demonstrate that delivery of therapeutics by CAR T cells can improve the safety profile of the therapeutic. Chapter 4 of this thesis explores strategies to increase the targeting capacity of CAR T cells by building logic-gated CARs. Finally, chapter 5 will describe work in imaging CAR T cells specifically, longitudinally, and non-invasively through PET imaging. Our results demonstrate the flexibility of VHHs in CAR T cell engineering and the potential of VHH-based CAR T cells to target the tumor microenvironment, modulate the tumor microenvironment, and treat solid tumors.

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