BIOGRAPHICAL SKETCH

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NAME: **Chen, Mingnan**

eRA COMMONS USER NAME: MINGNAN

POSITION TITLE: Associate Professor (tenured) of Pharmaceutics, College of Pharmacy, University of Utah

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date (MM/YYYY)	FIELD OF STUDY
Jimei University, Fujian, China	BS	07/1996	Aquaculture
Peking University, Beijing, China	MS	07/1999	Biology
University of Connecticut, Storrs, CT	PhD	08/2007	Pharmaceutics/Immunology
Duke University, Durham, NC	Postdoctoral	12/2011	Bioengineering/Drug Delivery

A. Personal Statement

I am a tenured, Associate Professor in the Department of Pharmaceutics and Pharmaceutical Chemistry at the University of Utah. My research platform is focused on developing protein- and peptide-based therapeutics for immunological disorders and cancer. I have a broad training background at the interface of protein engineering, immunology, and pharmaceutics. My previous research experience and accomplishments have laid groundwork to succeed in protein therapeutic development for autoimmune diseases and cancer. First, I have developed a therapeutic strategy for autoimmune diseases - the depletion of PD-1$^+$ cells. Through this research process, I developed not only protein tools to execute the depletion but also methodology to characterize the efficiency and impact of the depletion. Our data help to expand the understanding of PD-1 and PD-1 immune checkpoint in different types of cells and biological contexts. Further, I gained insight on the systemic impact of the depletion of PD-1$^+$ cells and recognized the impact is highly context-specific and likely short-term because of the dynamic nature of PD-1 expression **[Ref 1 & 2]**. Second, I have developed polypeptide-based drug delivery system for cancer therapeutics including vaccines and small molecule drugs. The experience offered me opportunities to get familiar with melanoma, lymphoma, and breast cancer models. I also leverage the experience to built up my expertise in the *in vitro* and *in vivo* characterization of the efficacy of cancer therapeutics **[Ref 3 & 4]**. I have served as Principal Investigator and Co-Investigator on multiple extramural awards from NIH, NMSS, and other foundations and successfully administered these funded projects (e.g. staffing, budget, collaboration, technology licensing). As a result of these research management experiences, I am aware of the importance of frequent communication among collaborators, of listening to and responding clinical needs, and of planning research project realistically in terms of time, budget, and alternative strategies.

The following are ongoing and recently completed projects I would like to highlight:

5R01AI139535 Chen M (PI) 01/25/19-12/31/23
NIH/NIAID
Targeted depletion of programmed death-1 positive (PD-1+) cells, a method that not only stops autoimmune attack but also preserves adaptive immunity
Relevance to Proposal: The knowledge, research tools, methods of the PD-1$^+$ cell depletion that are derived from this R01 project will be used to strengthen the design of the proposed project.

GR-1807-31630 Chen M (PI) 04/01/19-03/31/22
National Multiple Sclerosis Society
Understanding and utilizing the role of programmed death 1-positive (PD-1+) cells in multiple sclerosis
Relevance to Proposal: Results of this NMSS project will expand our knowledge on the systematic impact of the PD-1$^+$ cell depletion.

Melanoma Center Research Award Chen M (PI) 10/01/20-09/31/22
Huntsman Cancer Institute / University of Utah
β2M- and TAPBPR-enabled CTL epitope loading to tag melanoma cells and trigger immune elimination

Relevance to Proposal: Through this project, I am building collaborations with melanoma research community at the University of Utah including Dr. Matt VanBrocklin.

5R21EB024083 Chen M (PI) 03/01/17-12/31/19
NIH/NIBIB
Enhancing Cytotoxic T Lymphocyte (CTL) Responses by Directly Loading CTL Epitope Vaccines onto MHC Class I Complexes on the Dendritic Cell Surface
Relevance to Proposal: Through this project, I gained experience in evaluating efficacy of melanoma therapeutics and my team also acquired experience to quantify protein-to-protein by the SPR.

5R00CA153929 Chen M (PI) 08/01/12-07/31/16
NIH/NCI
Inhibition of Metastasis-initiating Cells by Chimeric Polypeptide Nanoparticles
Relevance to Proposal: Through this project, I acquired a full range of experiences in designing, developing, and characterizing cancer therapeutics including determining their cytotoxicity, maximum tolerated doses, pharmacokinetics, tumor suppression effect, etc. Such experiences are instrumental for me to design, execute, and trouble-shoot the proposed project of cancer therapeutics development.

The following are publications that highlight my experience and qualifications for this proposal:

1. Zhai Y, Moosavi R, **Chen M**. Immune Checkpoints, a Novel Class of Therapeutic Targets for Autoimmune Diseases. *Front Immunol.* 2021;12:645699. PMCID: PMC8097144
2. Zhao P, Wang P, Dong S, Zhou Z, Cao Y, Yagita H, He X, Zheng SG, Fisher SJ, Fujinami RS, **Chen M**. Depletion of PD-1-positive cells ameliorates autoimmune disease. *Nat Biomed Eng.* 2019 Apr;3(4):292-305. PMCID: PMC6452906
3. Zhao P, Atanackovic D, Dong S, Yagita H, He X, **Chen M**. An Anti-Programmed Death-1 Antibody (alphaPD-1) Fusion Protein That Self-Assembles into a Multivalent and Functional alphaPD-1 Nanoparticle. *Mol Pharm.* 2017 May 1;14(5):1494-1500. PMCID: PMC5601012
4. Zhao P, Xia G, Dong S, Jiang ZX, **Chen M**. An iTEP-salinomycin nanoparticle that specifically and effectively inhibits metastases of 4T1 orthotopic breast tumors. *Biomaterials.* 2016 Jul;93:1-9. PMCID: PMC4844807

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022	Ad hoc Reviewer, GDD, CNBT, CMIA Peer Review Committees, NIH
2021	Member, Peer Review Panel, PPMRP, Department of Defense (DoD)
2021	Member, NCI SEP-7 Peer Review Committee, NIH
2021	Ad hoc Reviewer, Nanotechnology Peer Review Committee, NIH
2020	Member, ZAI1-BLG-W-S1, Emergency Award (R01/R21) for COVID-19/SARS-CoV-2 Peer Review Committee, NIH
2020	Guest Editor, *Crit Rev Immunotheranostics, Theranostics*
2019-present	**Associate Professor** (tenured), Department of Pharmaceutics and Pharmaceutical Chemistry, College of Health, University of Utah, Salt Lake City, UT
2018-present	Member, American Chemical Society
2018	Member, Breast Cancer Research Program (BCRP) Peer Review Panel, DoD
2018	Grant Reviewer, ZonMw TOP Grants, The Netherlands Organisation for Scientific Research
2018	Grant Reviewer, King Abdullah International Medical Research Center (KAIMRC), Saudi Arabia
2014-present	Member, Experimental Therapeutics, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT
2014-present	Faculty Member, Cancer Immunotherapy Program, University of Utah, Salt Lake City, UT
2015-present	Member, Chinese American Society of Nanomedicine and Nanobiotechnology
2015	Session Chair, 17th International Symposiums on Recent Advances in Drug Delivery Systems
2012-2019	Assistant Professor, Department of Pharmaceutics and Pharmaceutical Chemistry, College of Health, University of Utah, Salt Lake City, UT
2013	Session Chair, 16th International Symposiums on Recent Advances in Drug Delivery Systems

2011	Discussion Panelist, *A Career in Cancer Nanotechnology* Discussion Panel, Annual NCI Alliance for Nanotechnology in Cancer Investigators' Meeting
2010-present	Ad hoc Reviewer, *Nat Biomed Eng* | *Adv Drug Deliv Rev* | *J Control Release* | *Adv Health Mater* | *Adv Funct Mater* | *Cancer Res* | *Biomater* | *Theranostics*
2009-present	Member, American Association for Cancer Research

Honors

2020	Honoree, VITAE Speaker, Senior Vice President for Health Sciences Research and Education Units, University of Utah
2019	Recipient, Poster Award, Nature Conference: Engineering Biology for Medicine
2019	Selected Speaker, Gordon Research Conference, Cancer Nanotechnology
2015	Scholar, Vice President's Clinical & Translational (VPCAT) Research Scholars Program, Senior Vice President for Health Sciences Education Unit, University of Utah
2010-2015	Recipient, NIH Pathway to Independence Award in Cancer Nanotechnology Research (K99CA153929/R00CA153929), NIH
2010	Honorable Mention, Student Travel Achievement Recognition, Society for Biomaterials
2009	Recipient, Citizens Advisory Council Poster Prize, Cancer Center Annual Meeting, Duke University
2009	Recipient, Scholarship Award, 18th Annual Short Course on Experimental Models of Human Cancer, the Jackson Laboratory
2003-2005	Predoctoral Fellow, Boehringer-Ingelheim Pharmaceuticals, Inc. Predoctoral Fellowship, University of Connecticut
2001-2005	Predoctoral Fellowship, University of Connecticut
1996	Recipient, Honor of Excellence for BSc Thesis, Jimei University

C. Contribution to Science

1. **Development of a New Therapeutic Strategies; The Depletion of PD-1 Positive ($^+$) Cells:** PD-1 was discovered as a receptor of the PD-1 immune checkpoint more than 20 years ago. Previously, therapeutic strategies around PD-1 rely on the knockout of PD-1 and the blockade of the PD-1 checkpoint. Two years ago, my team hypothesized and proved that PD-1 could be used as a biomarker to identify pathogenic cells. Our results shown that PD-1 is a powerful biomarker for autoreactive effector lymphocyte in autoimmune disorder, including type-1 diabetes and experimental autoimmune encephalomyelitis (EAE). Depletion of PD-1$^+$ cell in the context of autoimmune diseases reduced pathogenic immune cells, allowed mice with EAE to recover, and delayed the onset of type-1 diabetes. Meanwhile, our results also evidenced that the depletion does not affect immune repertoire or cause long-term immune deficiency because the vast majority of lymphocyte (naive lymphocytes) are PD-1$^-$ **[a]**. Our findings above instigate our curiosity to critique the relationship between immune checkpoint and autoimmune disease therapeutics, which eventually turns into a review article**[b]**. More recently, we confirmed the depletion of PD-1$^+$ cell may be used as an approach to treat cancer. We found this approach eliminate T cell lymphoma cells and allowed the mice with the tumor to survive throughout the entire period of the study **[Unpublished data]**. Our work serves as the preliminary data in support of this R21's proposed aims and evidences the first steps towards our development of a new therapeutic strategy for cancer and autoimmune diseases by targeted depletion of PD-1$^+$ cell.
   a. Zhao P, Wang P, Dong S, Zhou Z, Cao Y, Yagita H, He X, Zheng SG, Fisher SJ, Fujinami RS, **Chen M**. Depletion of PD-1-positive cells ameliorates autoimmune disease. *Nat Biomed Eng.* 2019 Apr;3(4):292-305. PMCID: PMC6452906
   b. Zhai Y, Moosavi R, **Chen M**. Immune Checkpoints, a Novel Class of Therapeutic Targets for Autoimmune Diseases. *Front Immunol.* 2021;12:645699. PMCID: PMC8097144

2. **Development of Drug Carriers for Cancer Therapeutics:** My contributions in this direction may be categorized into three classes although they share one theme: devising drug delivery systems to improve cancer therapeutics for better efficacy, lower side effect, or bother. Regarding the first class, I designed and generated polypeptide-based nanoparticle carriers to deliver cancer therapeutics, doxorubicin and salinomycin **[a-b]**. These carriers increase solubility of their drug payloads, expand the maximum tolerated doses of drugs, enable doxorubicin to eradicate murine colon tumors, and stop metastasis from clinically

relevant murine orthotopic breast tumors in the case of salinomycin. Overall, these carriers result in significantly longer survival for treated mice than those mice receiving free drugs. Regarding the second class, I designed and generated polypeptide-based nanoparticle carriers for vaccines that induce protective and therapeutical T cell-mediated immune responses. By optimizing stability, transport routes, intra-dendritic cell trafficking, release mechanisms of the vaccines, the carriers boosted T cell responses so that they are strong enough to eliminate melanoma cells from the mouse body **[c]**. Regarding the third class, I designed and generated nanoparticle carriers to deliver blocking anti-PD-1 antibodies. More importantly, these carriers are intended to increase the access of the antibodies to tumor-reactive T cells but limiting the access to auto-reactive T cells. The goal is to reduce immune-related adverse events (irAEs) including autoimmune side effects of the anti-PD-1 antibodies through altering the partition of the antibodies between different subpopulations of T cells **[d]**. In summary, the contributions responded to the needs to improve these cancer therapeutics or potential cancer therapeutics.

a. MacKay JA, **Chen M**, McDaniel JR, Liu W, Simnick AJ, Chilkoti A. Self-assembling chimeric polypeptide-doxorubicin conjugate nanoparticles that abolish tumours after a single injection. *Nat Mater.* 2009 Dec;8(12):993-999. PMCID: PMC2862348
b. Zhao P, Xia G, Dong S, Jiang ZX, **Chen M**. An iTEP-salinomycin nanoparticle that specifically and effectively inhibits metastases of 4T1 orthotopic breast tumors. *Biomaterials.* 2016 Jul;93:1-9. PMCID: PMC4844807
c. Dong S, Subramanian S, Parent KN, **Chen M**. Promotion of CTL epitope presentation by a nanoparticle with environment-responsive stability and phagolysosomal escape capacity. *J Control Release.* 2020 Dec 10;328:653-664.
d. Zhao P, Atanackovic D, Dong S, Yagita H, He X, **Chen M**. An Anti-Programmed Death-1 Antibody (alphaPD-1) Fusion Protein That Self-Assembles into a Multivalent and Functional alphaPD-1 Nanoparticle. *Mol Pharm.* 2017 May 1;14(5):1494-1500. PMCID: PMC5601012

3. **Innovation of Protein and Polypeptide Materials:** Although adverse immunogenicity of polypeptide and protein materials compromises their applications in medicine **[a]**, the evaluation of immunogenicity is rarely a priority during the development of these materials. Evaluation is usually carried out only after the physicochemical and functional properties of the materials are well established. We used an unconventional practice in our polypeptide development that incorporated both functionality and immunogenicity criteria in the design of polypeptides from the very beginning. Using this practice, we created immune-tolerant elastin-like polypeptides (**iTEPs**) that are both non-immunogenic and possess a thermally-induced inverse phase transition, a signature property of elastin-like polypeptides **[b-c]**. iTEPs were created through a completely new polypeptide engineering practice and are the first polypeptides of their kind.
   a. Kontos S, Hubbell JA. Drug development: longer-lived proteins. *Chem Soc Rev.* 2012 Apr 7;41(7):2686-2695.
   b. Cho S, Dong S, Parent KN, **Chen M**. Immune-tolerant elastin-like polypeptides (iTEPs) and their application as CTL vaccine carriers. *J Drug Target.* 2016;24(4):328-339. PMCID: PMC4813525
   c. **Chen M**, Cho HJ, Wang P, Dong S, Zhao P, Inventors; University of Utah Research Foundation, assignee. Immune Tolerant and Non-Immune Tolerant Elastin-Like Recombinant Peptides and Methods of Use. United States patent US 20180289830. 2018 Nov 8. World Patent WO 2016/196249. 2016 Aug 12.

4. **Investigation of the Major Histocompatibility (MHC) Class I Antigen Presentation Pathway:** MHC class I antigen presentation is a critical immunological event leading to cytotoxic T lymphocyte (CTL)-mediated immunity against intracellular pathogens and cancer. At the beginning of my PhD study, tapasin (an endoplasmic reticulum-resident protein) was just discovered as one component of the MHC class I epitope loading complex **[a]**. However, tapasin was not biochemically characterized and the working mechanisms of tapasin were not clear. Through my PhD study, I first characterized tapasin and defined its domain structures **[b]**. Then, I established an *in vitro* epitope loading complex consisting of tapsin and MHC class I molecules. Using this model, I elucidated how tapasin quality-controlled epitope loading for the MHC class I presentation and how the control impacted CTL immunity **[c]**. The publication summarizing the study was recommended as a “Must Read” publication by *Faculty 1000 Biology*. In addition to tapasin, I also contributed to studies of calreticulin, another component of the MHC class I epitope loading complex **[d]**.
   a. Sadegh-Nasseri S, **Chen M**, Narayan K, Bouvier M. The convergent roles of tapasin and HLA-DM in antigen presentation. *Trends Immunol.* 2008 Mar;29(3):141-147. PMCID: PMC3075112

b. **Chen M**, Stafford WF, Diedrich G, Khan A, Bouvier M. A characterization of the lumenal region of human tapasin reveals the presence of two structural domains. *Biochemistry.* 2002 Dec 10;41(49):14539-14545.
c. **Chen M**, Bouvier M. Analysis of interactions in a tapasin/class I complex provides a mechanism for peptide selection. *EMBO J.* 2007 Mar 21;26(6):1681-1690. PMCID: PMC1829385
d. Tan Y, **Chen M**, Li Z, Mabuchi K, Bouvier M. The calcium- and zinc-responsive regions of calreticulin reside strictly in the N-/C-domain. *Biochim Biophys Acta.* 2006 May;1760(5):745-753.

Complete List of Published Work in MyBibliography

https://www.ncbi.nlm.nih.gov/sites/myncbi/mingnan.chen.1/bibliography/49632869/public/?sort=date&direction=descending