Stem Cell and 3D Biofabrication Lab

Dr. Kaiming Ye

Professor & Department Chair

Biomedical Engineering

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Biography

Dr. Kaiming Ye is Professor and Department Chair of Biomedical Engineering and Director of Center of Biomanufacturing for Regenerative Medicine at the Binghamton University (BU), State University of New York (SUNY). He is one of the top most distinguished and accomplished leaders in the field of Medical and Biological Engineering. He is fellow of AIMBE and senior member of IEEE. His scholarly contributions to the field include the development of the concept of advanced biomanufacturing and his leadership role in promoting and growing the field of the advanced biomanufacturing. He is well-known for his work in bioprinting and tissue biofabrication, in particular the biofabrication of human pancreatic islets from pluripotent stem cells such as iPSCs. His work in advanced biomanufacturing was featured as a cover story of ASEE PRISM journal. He has invented fluorescent nanosensors for continuous glucose monitoring for type-1 diabetic patients. His work in glucose sensors was featured in the Pittsburgh Post-Gazette. He invented recombinant yeast-based influenza vaccines. His current work includes the development of cancer immune therapeutic vaccines. His research has been continuously supported by NIH, NSF, JDRF, ABI and industries. He has chaired and co-chaired a number of international conferences and has delivered keynote/plenary speech in numerous international and national conferences. He co-organized more than 10 workshops, including two WTEC studies: “Global Assessment of Stem Cell Science and Engineering” and “Global Assessment of Advanced Biomanufacturing” to promote and grow the field of advanced biomanufacturing, He serves as Editor-in-Chief, Executive Editor, Associate Editor, and member of Editorial Boards of 13 journals. He is also a highly accomplished administrator and has contributed significantly to the national policy-make in science and engineering. During his tenure at NSF, he directed a biomedical engineering program, making funding decisions and implementing post-award management. He was member of a number of interagency working groups, including the Interagency Workgroup for Neuroscience, Interagency Modeling and Analysis Workgroup, and Multiagency Tissue Engineering and Regenerative Medicine Workgroup. In addition, he was involved in NSF CIF21 IGRET program, Cyber-Enabled Science and Engineering Program, NIH/NSF joint program on interface between physics and life science, and NIH/NCI-NSF Physicals and Engineering Sciences in Oncology program. Finally, he is a highly accomplished educator in biomedical engineering. As chair of Biomedical Engineering Department at BU, he led the growth of the Department.

Selected Professional Activities and Awards

- Fellow, American Institute of Medical and Biological Engineering (AIMBE), 2014
- Senior Member, IEEE, 2013

- Council Chair, Biomedical Engineering Society Advanced Biomanufacturing Special Interest Group, 2014-2018
- Member, Biomedical Engineering Society Awards Committee, 2017-2019
- Member, NIH/NIDDK Building a Kidney Consortium External Advisory Committee, 2016~
- Member, Regenerative Medicine Standards Coordinating Body (SCB), May 2016~
- Chair, Advisory Board of School of Biomedical Engineering, Shanghai Jiaotong University, China, 08/13~present
- Subject Matter Expert, NSF/NIST funded Manufacturing MForsight Think-Tank, 2015~2016
- Member, Executive Committee, the Clinical Translational Science Institute, Medical School, University of Rochester, 2013~
- 2016 "Career Champion" award, Binghamton University, SUNY, New York
- Member, Scientific Advisory Committee, 2017 International Conference on Biofabrication, Oct. 15-18, 2018, Beijing, China
- Workshop Organizer and Chair: "Advanced Biomanufacturing", 2016 ASME Nano-engineering for
- Featured at the cover story entitled "Fit to Print" at February Issue of Prism by the American Society for Engineering Education (ASEE), February 2015
- Conference Co-Chair: 2016 Annual Meeting of Cell and Molecular Engineering and Advanced Biomanufacturing, New Orleans, LA, January 12-15, 2016
- Conference Chair, "NIH-NSF Joint Workshop for Integrative Additive Biomanufacturing and Tumor Engineering", Bethesda, MD, April 1-2, 2015
- Member, Scientific Advisory Board for Tissue Engineering and Regeneration Medicine International Society-Meeting—America, Washington, DC, USA, December 12-15, 2014
- Chair, Advisory Board, School of Biomedical Engineering, Shanghai Jiaotong University, 2014-present
- Member, Advisory Board of Joint School of Biomedical Engineering, Chongqing University and the Third Military Medical University, China, 05/12~07/14
- Section Co-organizer and Chair, Bioinspired Manufacturing, 2014 World Congress of Biomechanics, Boston, Nov, 25-28, 2014
- Member, SUNY Health Network Steering Committee, 2013
- Member, Scientific Advisory Committee, 2013 Tissue Engineering and Regenerative Medicine International Society--Asia annual Meeting, Shanghai, China, October 23-26, 2013
- Member, Conference Organizing Committee, the 3rd World Congress on Cell Science & Stem Cell Research, Baltimore, November 20-22, 2013
- Associated Editor, the 6th International IEEE EMBS Neural Engineering Conference, San Diego, November 6-8, 2013
- Member, State University of New York Health Now Network of Excellence Steering Committee, 2013~
- Member, Organizing Committee, International Conference and Exhibition on Biosensors & Bioelectronics, May 14-16, 2012, Las Vegas, USA
- International Advisory Board Member, "World Congress on Biotechnology", May 4-6, 2012, Hydenbad, India
- Topic organizer, "Nano drug Delivery and Nanomedicine" at the Track of "Nano engineering for Biology and Medicine", American Society for Mechanical Engineering, 2011 International Mechanical Engineering Congress & Exposition, Colorado, Denver, November 11-17, 2011
- Selected as an Organizing Committee Member, "International Conference on Clinical Research: Dermatology, Ophthalmology, and Cardiology", July 4-6, 2011, San Francisco, USA
- Served as an Organizing Committee Member, "International Conference and Exhibition on Biosensors and Bioelectronics", September 12-14, 2011, Baltimore, Maryland, USA
- Outstanding Research Award, 2010, 2009
- Member of Program Committee, 15th International Symposium on Smart Structures and Materials and Nanodestruction: Nanosensors and Microsensors for Bio-systems, San Diego, March 9-13, 2008.

- Member of Program Committee, the 15th International Symposium of SPIE Smart Structures and Materials and NDE for Health Monitoring and Diagnostics: nano-, micro-biosensors and systems, San Diego, March 9-13, 2008
- Member of Program Committee, 14th International Symposium of SPIE Smart Structures and Materials and NDE for Health Monitoring and Diagnostics: Nano, Micro-Biosensors and Systems, March 18-22, 2007.
- Board Member of IEEE's Five States Regional Meeting, 2007
- Featured in the 11/23/06Northwest Arkansas newspaper entitled "Scientist out to better diabetics' lives—Aim: steady blood sugar monitoring"
- Jin, S. and Ye, K. Nanoparticle-mediated drug delivery and gene therapy, Biotechnol. Prog. 23, 32-41, 2007, featured on the journal's most-accessed article
- Veetil and Ye, K. Development of immunosensors using carbon nanotubes. Biotechnol. Prog. 23, 517-531, 2007, featured on the journal's most-accessed articles
- Co-chairman of Combinatorial Bioengineering-Protein Display and Its Development Symposium of 2005 International Chemical Congress of Pacific Basin, Hawaii, USA, December 15-20, 2005.
- Featured in the Modern Drug Discovery entitled "GIP and Glucose" September 2003
- Featured in the 7/15/03 Pittsburgh Post-Gazette entitled "Pitt Researchers working on sensors that would monitor diabetics' blood sugar"
- Scientific consultant for McDonnel Boehnen Hulbert & Roche Diagnostics, Inc., 2002
- Distinguished Young Investigator Researcher Award, Ministry of Education, Science and Culture, Japan, 1999
- Distinguished Young Investigator Researcher Award, the Fellowship Foundation of Kyushu Institute of Technology, Japan, 1999.
- Featured in May 1st, 1999 Japanese Economic Daily for the invention of a cell surface protein display system.
- Featured in May 21st, 1999 Japanese Industrial Newspaper for the research achievement of creating an intracellular metabolic reporter.

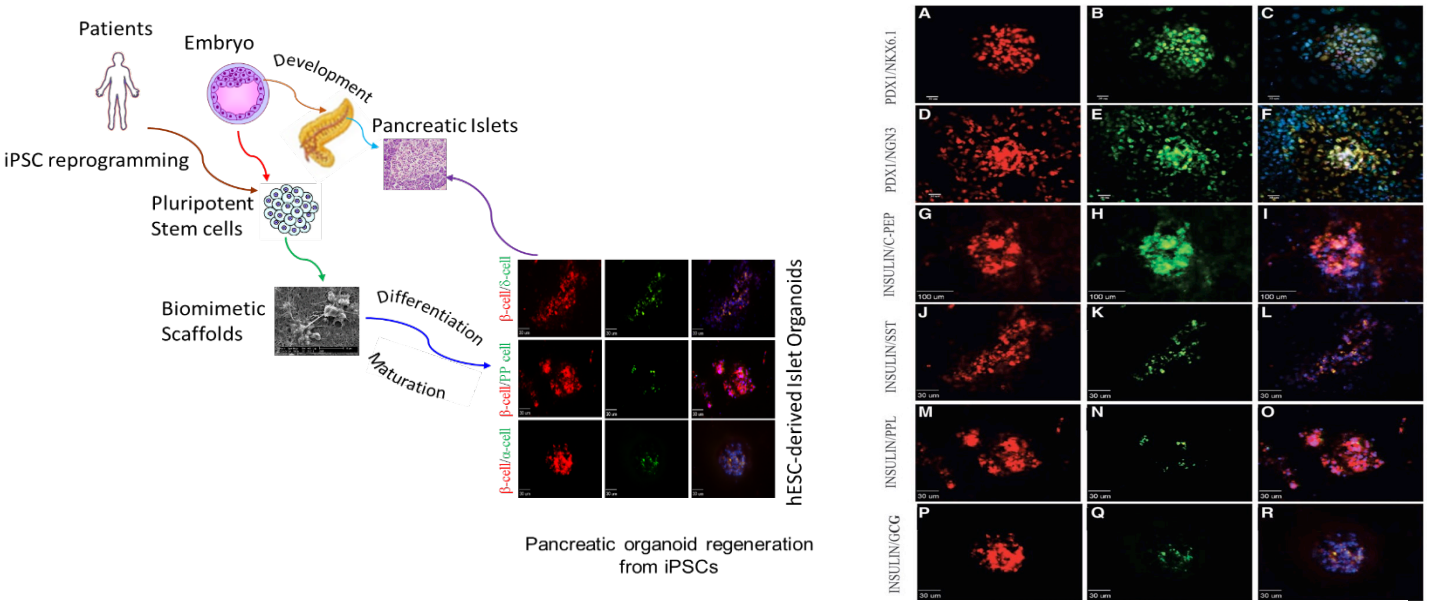
Research

- Vascularized pancreatic organoid development and 3D bioprinting
- Develop 3D biomimetic scaffolds for directing lineage-specific differentiation of human embryonic and induced pluripotent stem (ES/iPS) cells into clinically-relevant cell lineages such as insulin-secretion pancreatic beta cells and islet organoids for cell replacement therapy
- Construct bioinspired materials for wound healing and bone and neuron regeneration
- Create fluorescent nanosensors for in vivo tracking stem cell proliferation and differentiation
- Develop implantable glucose sensors for continuous blood glucose monitoring for diabetic patients
- Engineer fluorescence nanaosensors for real-time measurement of glucose transport in insulin-resistance tissues and cells by visualizing glucose dynamics in these cells through fluorescence lifetime imaging microscopy (FLIM) measurement

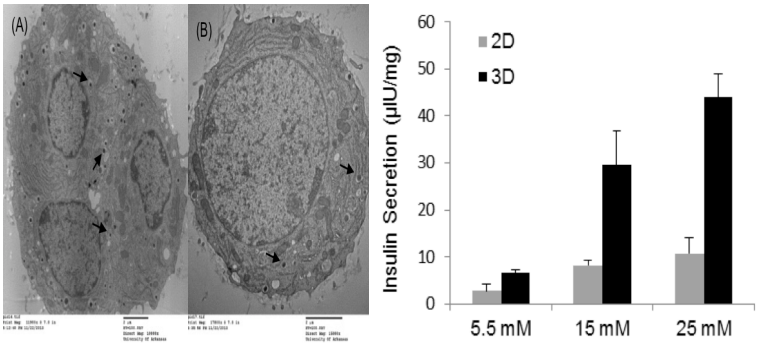
Research Programs:

- ***Human Pancreatic Islets Organoid Development from human pluripotent stem cells (HPSCs)—Hope for Diabetes treatment***

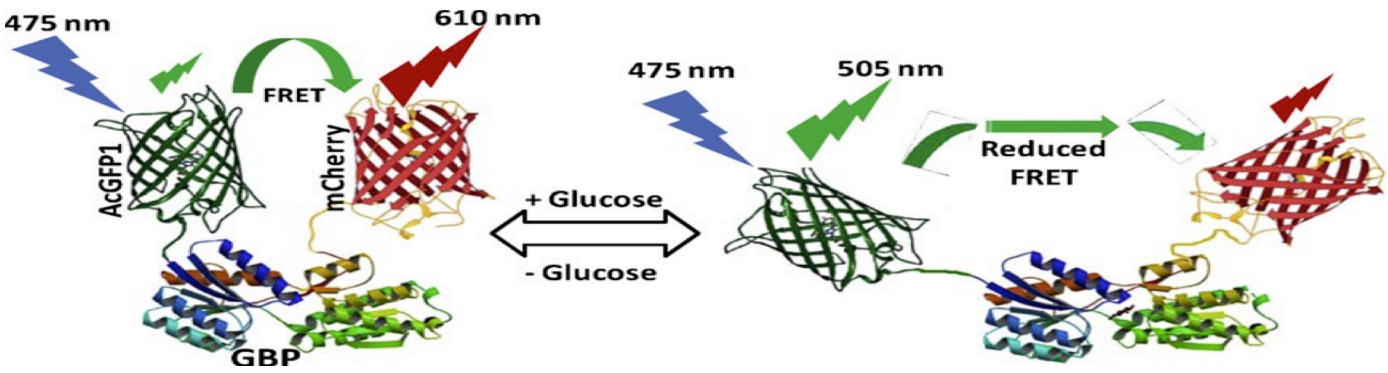
Islet transplantation brings a hope to diabetic patients who may one day be able to live normally without relying upon insulin-injection, frequent glucose monitoring and diet adjustment. However, the shortage of transplantable pancreatic islets has impaired the availability of this promising treatment for most patients. This lab focuses on the creation of transplantable islets, enabling the patients to restore their near-physiological insulin secretion capability.



Dual-color immunofluorescence microscopy of islet organoids differentiated from hESCs within CM scaffolds. Cell clustered formed at Stage IV within CM scaffolds were dual-color stained using primary antibodies against PDX1 (A and D), NKX6.1 (B), NGN3 (E), Insulin (G, J, M, and P), C-peptide (H), Somatostatin (K), Pancreatic Polypeptide (N), and Glucagon (Q) and secondary antibodies as listed in **Table 2**. Cells were counterstained with DAPI (blue). The cell clusters were directly examined under a fluorescence microscope. (C), (F), (I), (L), (O), and (R) are merged immunofluorescence micrographs. Scale bar: (A-F, J-R), 30 μm and (G-I), 100 μm. (S) and (T) are negative controls. These cell clusters were stained with either FITC (green) or TRITC (red) conjugated secondary antibodies.



Glucose-responsive, insulin-secretion of islet organoids generated from hESCs within C-M scaffolds. (A)-(B) TEM detection of insulin secretory granules (black arrows) in β cells generated from hESCs in 2D (A) and 3D conditions (B). Scale bar: 2 μm. (C) Determination of insulin secretion from hESCs-derived cell clusters upon glucose challenges through insulin ELISA. The insulin secretion was determined as μIU (international unit) insulin per mg cellular proteins.



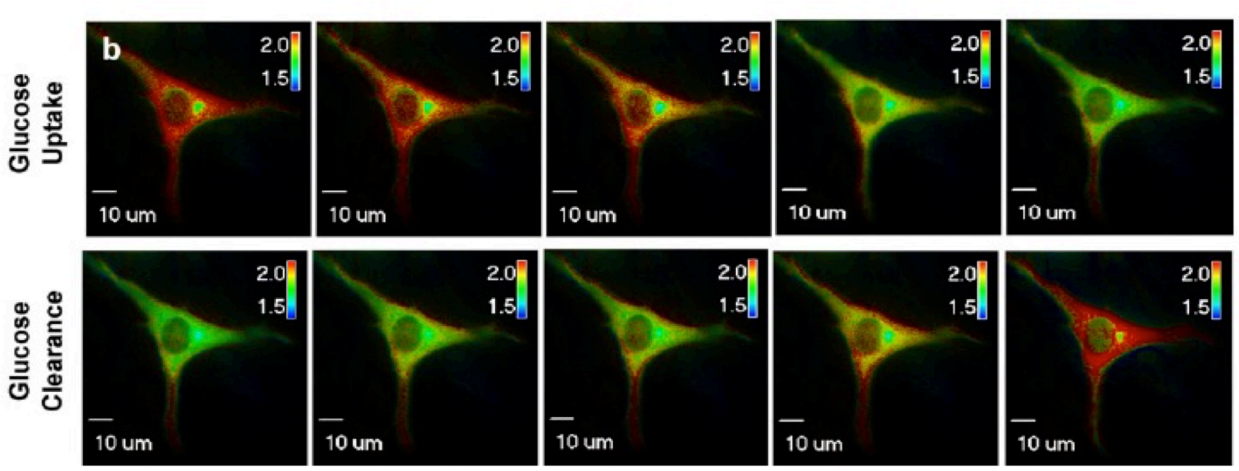
A molecular structure of FRET sensor proteins designed for continuous glucose monitoring. In this design, a glucose-binding protein (GBP) is sandwiched with AcGFP1 at its N-terminus and mCherry at its C-terminus. The GBP adopts an "open" form in the presence of glucose and a "close" form in the absence of glucose, leading to a change in the relative distance between AcGFP1 and mCherry and thereby altering the FRET efficiency between AcGFP1 and mCherry.

- ***Fluorescence nanosensors for continuous glucose monitoring for type-1 diabetic patients***

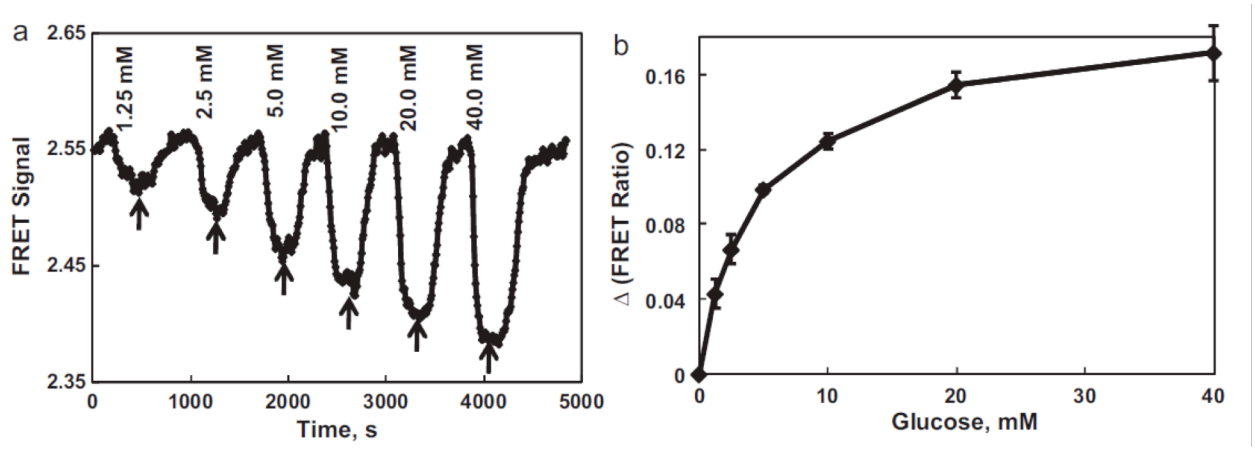
Diabetes mellitus is one of the major health care problems in the world. It has long been known that more frequent blood glucose monitoring can prevent many long-term complications associated with diabetes. However, the nature of the finger-stick glucose testing restricts its utility for maintaining strict levels of the blood glucose concentration. This dilemma has resulted in a worldwide effort to develop new glucose sensors for fast, painless, and convenient glucose monitoring. To respond to these challenges, we developed a new and novel glucose sensor that enables continuous glucose monitoring. The sensor was developed based on our invention on a molecular design of a glucose indicator protein (GIP). The GIP was constructed by integrating an optical signal transduction function directly into a glucose binding protein (GBP). Our strategy is to incorporate fluorescence reporter groups into a GBP in such a manner that the spatial separation between the fluorescence moieties change upon glucose binding, generating a signal for optical detection. This new molecular design capitalized on the FRET method that has been widely used in bioassays. This new design is a paradigm shift in glucose sensor development that has long been focused on the use of GOX and off-time glucose monitoring. The realization of this new sensor mechanism enabled continuous glucose monitoring, and could eventually supplant traditional finger-sticking glucose measurement by implanting these sensors beneath the skin. The original GIP was developed based on a wild type GBP isolated from *E. coli*. It responds to glucose in a range on the order of 10 μM of glucose. To employ this GIP for monitoring blood glucose concentrations, its operational range needs to be elevated to an order of mM. After analyzing the X-ray structure of the GBP, we identified the mutation sites that could shift the glucose binding constant from μM to mM. Using site-directed mutagenesis, we successfully created a GBP mutant which glucose binding constant is about 7.86 mM. The sugar binding assay indicated that it is highly specific for glucose binding. A microsensor developed based on this GIP has an optional range from 0 to 32 mM of glucose and its response time to sudden glucose changes is within 100s, suitable for continuous glucose monitoring.

This sensor can provide real-time monitoring of blood glucose concentrations while helping patients avoid painful and inconvenient finger-sticking or skinpricking glucose monitoring. They can potentially be implanted beneath the skin for continuous glucose monitoring. The development and commercialization of these technologies will eventually get rid of finger-sticking glucose measurements, improving the life qualify of diabetic patients.

- *Fluorescence microscopy measurement of single molecule in living cells.* Using another GBP mutant which glucose constant is at about 131 μM, we developed a fluorescence nanosensor that allows for the visualization of intracellular glucose in living cells. The integration of a gene encoding this fluorescence nanosensor allows for biosynthesis of the sensor by cells for continuous reporting changes in intracellular glucose concentrations in response to changes in extracellular glucose concentrations. Both FRET and a frequency-domain (FD) FLIM measurement were developed for visualizing of glucose dynamics within living cells. With these measurements, we determined the glucose uptake and clearance rates in murine skeletal muscle cells. They are about 31 and 101s, respectively. We also discovered uniform distribution of glucose within cytoplasm with high glucose concentration in the region close to membrane and low glucose concentration in a region close to cell nucleus. This sensor enables direct and real-time monitoring of glucose transport in insulin-sensitive cells by visualizing glucose dynamics in these cells through FRET-FLIM imaging microscopy measurement. It can be used for high-throughput screening of anti-diabetes drugs that target to glucose transporters in peripheral tissues that develop insulin-resistance. These sensors can also be employed for characterizing the underlying mechanisms responsible for the development of abnormal glucose transport in obese and diabetic patients. Data accumulated from these studies will



Visualization of intracellular glucose in single live cell with GIPi-Cys. Pseudo-colored ratiometric FRET images of cells cultured in different glucose concentrations. The murine myoblast cells (C2C12) were cultured in a medium



Continuous glucose monitoring through ratiometric FRET measurement with the GIPi-Thr sensor. (a) Buffers containing various glucose concentrations from 1.25 mM to 40 mM were flown through the sensor assembly and the FRET signals were recorded continuously every 6 s. The sensor was excited at 435 nm. Its emission at 475 and 525 nm were monitored with a luminescence spectrophotometer. The slit widths were set at 10 nm for both excitation and emission. The arrows indicate the flow of sugar-free bath into the sensor assembly. (b) CGM experiments were repeated (n = 3) and its glucose response curve was determined. The ratio reflects the differences between the peak height at a given glucose concentration and the baseline in CGM curve. The measurements were performed at room temperature.

provide insights into the pathogenesis of diabetes

Selected Publications

Report:

- Drew, S., Bao, G., Bettinger, C., Leong, K., Peshwa, M, and Ye, K. (2015) "WTEC Report: Global Assessment of Biological Engineering & Manufacturing", World Technology Evaluation Center. This Report was supported by NSF
- Abraham, E., Bertram, T., Harris, L., Matosevic, S., Ting, A., Vanek, P., Ye, K., Zhang, J., and Zylberberg, C. (2015) " Rapid Response Report: Biomanufacturing for Regenerative Medicine", MForesight—Alliance for Manufacturing Foresight Think-Tank, Supported by NSF and NIST
- Guest Editor, A special issue on biomanufacturing for regenerative medicine (2017), *ACS Biomaterials Science and Engineering*. 3(8)

Book

- Ye, K. and Sha Jin (2011) "Human Embryonic and Induced Pluripotent Stem Cells", Springer, Humana Press, New York, USA, ISBN 978-1-61779-266-3

Patent

- Ye, K. and Jin, S. (2010) "pH Insensitive Glucose Indicator Proteins", US 12/902725
- Schultz, J. and Ye, K. (2005) "System and Method for Detecting Bioanalytes and Method for Producing a Bioanalyte Sensor", US 2005/0118726A1
- Jin, S., Ye, K., and Bi, H., (2017) " Microenvironments for self-assembly of islet organoids from stem cell differentiation", US 62/479,095

Selected Peer-Reviewed Publications

- Wang, W., Jin, S., and Ye, K. (2017) "Development of islet organoids from H9 human embryonic stem cells in biomimetic 3D scaffolds", *Stem Cells and Development*, 26, 394-404
- Ye, K. and Sambanis, A. (2017) "Advanced Biomanufacturing: A Radical Manufacturing Paradigm Shift from Conventional, Centralized, Off-the-Shelf Production to On-Demand, Decentralized, Plug-and-Play Production of Cell- and Tissue-Based Products", *ACS Biomaterials Sci. Eng.*, 3(8), 1460-1461, DOI: 10.1021/acsbiomaterials.7b00535
- Ye, K, and Jin S. (2017) "From Stem Cells to Islets Organoids", *Stem Cells and Development*, 26, Cover Page.
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- Lei, H., Jin, S., Karlsson, E., Schultz-Cherry, S., Ye, K. (2016) "HA Surface Presented Yeast H5N1 Avian Influenza Vaccine", J. Immunol. Res., 2016, 1-12, *doi:10.1155/2016/4131324*
- Leach, J.C., Wang, A., Ye, K. Jin, J. (2016) "A RNA-DNA Hybrid Aptamer for Nanoparticle-Based Prostate Tumor Targeted Drug Delivery", *International Journal of Molecular Sciences*, 17, 380-391; doi:10.3390
- Wang L., Wang R., Kong B-W, Jin S., Ye, K. and Li, Y. (2015) "B cells Using Calcium Signaling for Specific and Rapid Detection of *Escherichia coli* O157:H7", *Sci. Rep. 5, 10598; doi: 10.1038/srep 10598*
- Bin He, Coleman, T., Genin, G.M., Glover, G., Xiaoping Hu, Johnson, N., Tianming Liu, Makeig, S., Sajda, P., Kaiming Ye (2013) "Grand Challenges in Mapping the Human Brain: NSF Workshop Report", *IEEE Transaction on Biomedical Engineering*, 60, 2983-2992
- Earls, J., Jin, S., and Ye, K. (2013) "Mechanobiology of human pluripotent stem cells", *Tissue Engineering, Part B*, 19(5), 420-430

- Jin, S. and Ye, K. (2013) Targeted Drug Delivery for Breast Cancer Treatment, *Recent Patents on Anti-Cancer Drug Discovery*, 8(2), 143-153
- Jin, S., Yao, H., Weber, J.L., Melkoumian, Z. K., Ye, K. (2012) "A synthetic xeno-free peptide surface for expansion and directed differentiation of human induced pluripotent stem cells", *PLoS One*, 7(11), e50880
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- Jin, S., Yao, H., Krisanarungson, P., Haukas, K., and Ye, K. (2012) Porous Membrane Substrates Offer Better Niches to Enhance the Wnt Signaling and Promote Human Embryonic Stem Cell Growth and Differentiation, *Tissue Engineering Part A*, 18, 13-14, 2012
- Jin, S., Peterson K., Ye, K. (2012) Determination of motilities of human pluripotent stem cells on various soft substrates. *J. Tissue Eng. Regen Med.* 6 (suppl 1), 195
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- Jin, S. Ellis, E., Veetil, JV, Yao, H., Ye, K. (2011) Visualization of HIV Protease Inhibition Using a Novel FRET Molecular Probe, *Biotechnol. Prog. 4, 1107-1114*
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- Garett, J.R., Wu, X., Sha, J. and Ye, K. (2008) pH-insensitive Glucose Indicators, *Biotechnol. Prog.* 24, 1085-1089
- J. Xie, K.R., Aatre, V.K., Varadan, J.V. Veetil, and K. Ye (2008) Synthesis of aligned carbon nanotubes by microwave chemical vapor deposition and investigation of their covalent bonding with antibodies for bio-applications. *International Journal of Nanoparticles*, 1, 119-135.
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