

Yoshihiro Ishikawa, MD, PhD, FACC, FACP, FAHA, FESC, FJCC,

Provost for Medical Affairs
Yokohama City University

Professor and Chair
Cardiovascular Research Institute
Yokohama City University School of Medicine
Yokohama 236-0004, JAPAN



Prof. Ishikawa attended medical schools in both Japan (Yokohama City University, Yokohama) and US (Yale Medical School, CT), and received his MD and PhD from Yokohama City University. He served as Assistant Professor at Columbia University and Harvard University. He also served as Professor as well as Attending Physician (Cardiology) at Rutgers University New Jersey Medical School for many years. Since 1998, he has been serving as the Chair of the Cardiovascular Research Institute of Yokohama City University School of Medicine. He also completed his tenure as Dean at Yokohama City University Graduate School of Medicine, and is now serving as the Provost for Medical Affairs of the Yokohama City University since 2018. He has published more than 220 papers in peer-reviewed journals. His research interest includes molecular cardiology, especially autonomic regulation and prostaglandin signal in the cardiovascular medicine, and its boundary medicine such as tissue engineering or oncology. He has been serving as an editorial member of many reputed journals, such as *Pharmacological Reviews*, *Cardiovascular Research*, or *Scientific Reports*. He has been honored as Fellow member of various academic societies in US, EU, and Japan.

A. EDUCATION

1984 MD Yokohama City University School of Medicine, Yokohama, Japan
1993 PhD Yokohama City University School of Japan, Yokohama, Japan

B. POSITIONS AND HONORS

Positions and Employment

1984-86 Intern and Resident in Medicine, Yokohama City University Hospital, Yokohama, Japan
1986-88 Clinical Fellow in Cardiology, Kanagawa Cardiovascular Center, Yokohama, Japan
1988-91 Research Fellow in Medicine (Cardiology), Massachusetts General Hospital, Boston, MA
1991-95 Assistant Professor of Pharmacology and Medicine (Cardiology)
College of Physicians and Surgeons of Columbia University, New York, NY
1995-97 Assistant Professor of Medicine, Brigham and Women's Hospital,
Harvard Medical School, Boston, MA
1997-2000 Associate Professor of Medicine and Pharmacology, Cardiovascular and Pulmonary Research Institute,
Drexel University College of Medicine, Pittsburgh, PA
1998-2000-04 Professor and Chair, Cardiovascular Research Institute Yokohama City University, Japan
Associate Professor of Cell Biology & Molecular Medicine and Medicine (Cardiology),
Rutgers University New Jersey Medical School, Newark, NJ
2005-12 Professor of Cell Biology & Molecular Medicine and Medicine (Cardiology),
Rutgers University New Jersey Medical School, Newark, NJ
2008-10 Dean, Yokohama City University Graduate School of Medicine, Japan
2015- Visiting Professor, Osaka University Graduate School of Frontier Bioscience,
2018- Provost for Medical Affairs, Yokohama City University

Honors:

1993 Medical Science Achievement Award, American Cyanamid Company
Young Investigators Award, Molecular Biology of the Hypertension and Failing Heart,
American Heart Association
1996 Finalist, 1996 Council on Circulation Cardiovascular Research Prize
1998 Established Investigator Award, American Heart Association

Medical License:

USA (New Jersey, Pennsylvania) and Japan

Fellowship Certification:

American College of Cardiology (FACC), American College of Physician (FACP), Royal Society of Medicine (FRSM), American Heart Association (FAHA), Japanese College of Cardiology (FJCC), European Society of Cardiology (FESC)

Editorial Boards (current):

Pharmacological Reviews (Associate Editor, American Society for Pharmacology and Experimental Therapeutics)

Cardiovascular Research (Consultant Editor, European Society of Cardiology)

Journal of Physiological Science (Chief Editor, Physiological Society of Japan)

Scientific Reports (Editorial Board in Cardiology, Nature Publishing)

Executive Appointments in Medical Societies:

2012- Vice President, the Japanese Physiological Society

2020-23 President-Elect, the Japanese Physiological Society

Board of Trustees (current): Japanese Circulation Society, Japanese Endocrine Society, Japanese Heart Failure Society, Japanese Cardiovascular Endocrine Society, Board of Directors: Japan Health Care Society, Japanese Pathophysiology Society,

Others: Congress President of the 90th annual meeting of the Japanese Physiological Society

C. SELECTED PUBLICATIONS

(Full publications since 2016 and selected ones from 228 peer-reviewed publications):

1. Ishikawa Y, Bianchi C, Nadal-Ginard B, and Homcy CJ: Alternative promoter and 5' exon generate a novel Gs-alpha mRNA. *J. Biol. Chem.* 265;8458-8462, 1990
2. Ishikawa Y, Katsushika S, Chen L, Halnon N, Kawabe J, and Homcy CJ: Isolation and characterization of a novel cardiac adenylylcyclase cDNA. *J. Biol. Chem.* 267;13553-13557, 1992
3. Katsushika S, Chen L, Kawabe J, Nilakantan R, Halnon N, Homcy CJ, and Ishikawa Y: Cloning and characterization of a sixth adenylylcyclase isoform: Types V and VI constitute a subgroup within the mammalian adenylyl cyclase family. *Proc. Natl. Acad. Sci. USA.* 89;8774-8778, 1992
4. Katsushika S, Kawabe J, Homcy CJ, and Ishikawa Y: In vivo generation of an adenylylcyclase isoform with a half-molecule motif. *J. Biol. Chem.* 268;2273-2276, 1993
5. Ishikawa Y, Sorota S, Kiuchi K, Shannon RP, Komamura K, Katsushika S, Vatner DE, Vatner SF, and Homcy CJ: Downregulation of adenylylcyclase types V and VI mRNA levels in pacing-induced heart failure. *J. Clin. Invest.* 93;2224-2229, 1994
6. Kawabe J, Iwami G, Ebina T, Ohno S, Katada T, Ueda Y, Homcy CJ, and Ishikawa Y: Differential activation of adenylyl cyclase by protein kinase C isoenzymes. *J. Biol. Chem.* 269;16554-16558, 1994
7. Tobise K, Ishikawa Y, Holmer SR, Im M-J, Newell JB, Yoshie H, Fujita M, Susannie EE, and Homcy CJ: Changes in type VI adenylylcyclase isoform expression correlate with a decreased capacity for cAMP generation in the aging ventricle. *Circ. Res.* 74;596-603, 1994
8. Kawabe J, Ebina T, Ismail S, Kitchen DB, Homcy CJ, and Ishikawa Y: A novel peptide inhibitor of adenylyl cyclase (AC): A peptide from type V AC directly inhibits AC catalytic activity. *J. Biol. Chem.* 269;24906-24911, 1994
9. Gaudin C, Ishikawa Y, Wight DC, Mahdavi V, Nadal-Ginard B, Wagner TE, Vatner DE, and Homcy CJ: Overexpression of Gsalpha protein in the heart of transgenic mice. *J. Clin. Invest.* 95;1676-1683, 1995
10. Iwami G, Kawabe J, Ebina T, Cannon PJ, Homcy CJ, and Ishikawa Y: Regulation of adenylyl cyclase by protein kinase A. *J. Biol. Chem.* 270;12481-12484, 1995
11. Iwase M, Bishop SP, Uechi M, Vatner DE, Shannon RP, Kudej RK, Wight DC, Wagner TE, Ishikawa Y, Homcy CJ, and Vatner SF: Adverse effects of chronic endogenous sympathetic drive induced by cardiac Gsalpha overexpression. *Circ. Res.* 78;517-524, 1996
12. Kawabe J, Toya Y, Schwencke C, Oka N, Ebina T, and Ishikawa Y: Soluble adenylyl cyclase from *Spodoptera frugiperda* (Sf9) cells: Purification and biochemical characterization. *J. Biol. Chem.* 271;20132-20137, 1996
13. Oka N, Yamamoto M, Schwencke C, Kawabe J, Ebina T, Ohno S, Couet J, Lisanti MP, and Ishikawa Y: Caveolin interaction with protein kinase C: Isoenzyme-dependent regulation of kinase activity by the caveolin scaffolding domain peptide. *J. Biol. Chem.* 272; 33416-33412, 1997
14. Uechi M, Osaka M, Asai K, Sato N, Wagner TE, Ishikawa Y, Vatner DE, Smith A, Hayakawa H, Shannon RP, Cohen RJ, Homcy CJ, and Vatner SF: Depressed heart rate variability and arterial baroreflex in conscious transgenic mice with overexpression of cardiac Gsalpha. *Circ. Res.* 82;416-423, 1998
15. Vatner DE, Asai K, Ishikawa Y, Wagner TE, Shannon RP, Homcy CJ, and Vatner SF: Overexpression of myocardial Gsalpha prevents full expression of catecholamine desensitization despite increased beta-adrenergic receptor kinase. *J.*

- Clin. Invest.* 101;1916-1922, 1998
16. Lader AS, Xiao Y-F, Ishikawa Y, Tomlinson J, Vatner DE, Vatner SF, Homcy CJ, and Cantiello HF: Cardiac Gsalpha overexpression enhances L-type calcium channels through an adenylyl cyclase independent pathway. *Proc. Natl. Acad. Sci. USA* 95;9669-9674, 1998
 17. Yamamoto M, Toya Y, Schwencke C, Lisanti MP, Myers Jr. MG, and Ishikawa Y: Caveolin is an activator of insulin receptor signaling. *J. Biol. Chem.* 273; 26962-26968, 1998
 18. Geng Y-J, Ishikawa Y, Vatner DE, Wagner TE, Bishop SP, Vatner SF, and Homcy CJ: Apoptosis of cardiac myocytes in Gsalpha transgenic mice. *Circ. Res.* 84;34-42, 1999
 19. Kim S-J, Yatani A, Vatner DE, Yamamoto M, Ishikawa Y, Wagner TE, Shannon RP, Homcy CJ, and Vatner SF: Differential regulation of inotropy and lusitropy in overexpressed Gsalpha myocytes through cAMP and Ca²⁺ channel pathways. *J. Clin. Invest.* 103; 1089-1097, 1999
 20. Asai K, Yang GP, Geng Y-J, Takagi G, Bishop S, Ishikawa Y, Shannon RP, Wagner TE, Vatner DE, Homcy CJ, and Vatner SF: Beta-adrenergic receptor blockade arrests myocyte damage and preserves cardiac function in the transgenic Gsalpha mouse. *J. Clin. Invest.* 104; 551-558, 1999
 21. Vatner DE, Yang G-P, Geng Y-J, Asai K, Yun JS, Wagner TE, Ishikawa Y, Bishop SP, Homcy CJ, and Vatner SF: Determinants of the cardiomyopathic phenotype in chimeric mice overexpressing cardiac Gsalpha. *Circ. Res.* 86: 802-806, 2000
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 23. Onda T, Hashimoto Y, Nagai M, Kuramochi H, Saito S, Yamazaki H, Toya Y, Sakai I, Homcy CJ, Nishikawa K, and Ishikawa Y: Type-specific regulation of adenylyl cyclase; selective pharmacological stimulation and inhibition of adenylyl cyclase isoforms. *J. Biol. Chem.* 276; 47785-47793, 2001
 24. Okumura S, Kawabe J, Takagi G, Lee L, Hong C, Liu J, Takagi I, Sadoshima J, Yatani A, Vatner DE, Vatner SF, and Ishikawa Y: Type 5 adenylyl cyclase disruption alters not only sympathetic, but also parasympathetic and calcium-mediated regulation of cardiac regulation. *Circ. Res.* 93: 364-371, 2003
 25. Minamisawa S, Wang Y, Chen J, Ishikawa Y, Chien K R, and Matsuoka R. Atrial chamber-specific expression of sarcolipin is regulated during development and by hypertrophic remodeling. *J. Biol. Chem.* 278:9570-9575, 2003.
 26. Okumura S, Takagi G, Kawabe J-I, Yang G, Lee M-C, Hong C, Liu J, Takagi I, Sadoshima J, Vatner DE, Vatner SF, and Ishikawa Y: Disruption of type 5 adenylyl cyclase gene preserves cardiac function against pressure overload. *Proc. Natl. Acad. Sci. USA.* 100:9986-90,2003
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 29. Oshikawa J, Ohtu K, Toya Y, Tsunematsu T, Hankins RW, Kawabe J, Minamisawa S, Umemura S, Hagiwara Y, and Ishikawa Y: Insulin resistance in skeletal muscles of caveolin-3 null mice. *Proc. Natl. Acad. Sci. USA* 101; 12670-12675, 2004
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 33. Yan L, Vatner DE, Ivessa A, Ge H, Chen W, Hirofani S, Ishikawa Y, Sadoshima J, and Vatner SF: Type 5 adenylyl cyclase disruption increases longevity and protect against stress. *Cell* 130:247-58, 2007.
 34. Okumura S, Vatner DE, Kurotani R, Bai Y, Gao S, Yuan Z, Iwatsub K, Ulucan C, Kawabe J, Ghosh K, Vatner FS, and Ishikawa Y: Disruption of Type 5 adenylyl cyclase enhances desensitization of cyclic adenosine monophosphate signal

- and increases Akt signal with chronic catecholamine stress. *Circulation* 116:1776-83, 2007
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 36. Tsutsumi Y, Horikawa YT, Jennings M, Kidd MW, Niesman IR, Yokoyama U, Head BP, Hagiwara Y, Ishikawa Y, Miyanochara A, Patel PM, Insel PA, Patel HH, and Roth DM: Cardiac specific overexpression of caveolin-3 induces endogenous cardiac protection by mimicking ischemic preconditioning. *Circulation* 118:1979-88, 2008
 37. Kheirbek MA, Beeler JA, Ishikawa Y and Zhuang X: A cyclic AMP pathway selectively required for reward prediction. *J. Neuroscience* 28:11401-11408, 2008
 38. Kheirbek M, Britt J, Beeler J, Ishikawa Y, McGehee D, and Zhuang X: Adenylyl cyclase type 5 is critical for corticostriatal plasticity and striatum-dependent learning. *J. Neuroscience* 29:12115-24, 2009
 39. Sato M, Honda T, Jiao Q, Kurotani R, Toyota E, Okumura S, Lanier SM, and Ishikawa Y: An involvement of activator of G protein signaling 8 on hypoxia-induced apoptosis of cardiomyocytes and its interaction with connexin 43. *J. Biol. Chem.* 284:31431-40, 2009
 40. Yokoyama U, Minamisawa S, Katayama A, Tang T, Suzuki S, Iwatsubo K, Iwasaki S, Kurotani R, Okumura S, Sato M, Yokota S, Hammond HK, and Ishikawa Y: Differential regulation of vascular tone and remodeling via stimulation of type 2 and type 6 adenylyl cyclases in the ductus arteriosus. *Circ. Res.* 106;1882-92, 2010
 41. Suzuki S, Yokoyama U, Abe T, Kiyonari H, Yamashita N, Kurotani R, Sato M, Okumura S, and Ishikawa Y: Differential roles of Epac in regulating cell death in neuronal and myocardial cells. *J. Biol. Chem.* 285;24248-59, 2010
 42. Kurotani R, Okumura S, Matsubara T, Yokoyama U, Buckley JR, Tomita T, Kezuka K, Nagano T, Esposito D, Taylor TE, Gillette WK, Ishikawa Y, Abe H, Ward JM, and Kimura S: Secretoglobin 3A2 suppresses bleomycin-induced pulmonary fibrosis by TGFbeta signaling down-regulation. *J. Biol. Chem.* 286: 19682-92, 2011
 43. Sato M, Hiraoka M, Suzuki H, Yunze B, Kurotani R, Yokoyama U, Okumura S, Cismowski MJ, Lanier SM, and Ishikawa Y: TFE3 is an activator of G protein signaling for nuclear Galp ha16 subunit in the cardiac hypertrophy. *J. Biol. Chem.* 286:17766-76, 2011
 44. Lai L, Yan L, Gao S, Hu CL, Hui G, Davidow A, Park M, Bravo C, Iwatsubo K, Ishikawa Y, Auwerx, J, Sinclair D, Vatner SF, and Vatner DE: Type Type 5 Adenylyl Cyclase Increases Oxidative Stress by Transcriptional Regulation of MnSOD via the Sirt1/FoxO3a Pathway. *Circulation* 127:1692-701, 2013
 45. Eijkelkamp N, Linley JE, Torres JM, Bee L, Dickenson AH, Gringhuis M, Minett MS, Hong GS, Lee E, Oh U, Ishikawa Y, Zwartkuis FJ, Cox JJ, and Wood, JN: A role for Piezo2 in EPAC1-dependent mechanical allodynia. *Nature Commun.* 4:1682, 2013
 46. Wang H, Heijnen CJ, van Velthoven CTJ, Willems HLDM, Ishikawa Y, Zhang X, Sood AK, Vroon A, Eijkelkamp N, and Kavelaars A: Balancing GRK2/ Epac1 levels prevents and relieves chronic pain. *J. Clin. Invest.* 123:5023-5034, 2013
 47. Yokoyama U, Minamisawa S, Shioda A, Ishiwata R, Jin MH, Masuda M, Asou T, Sugimoto Y, Aoki H, Nakamura T, and Ishikawa Y: Prostaglandin E2 inhibits elastogenesis in the ductus arteriosus via EP4 signaling. *Circulation* 129:487-96 2014
 48. Ishiwata R, Yokoyama U, Matsusaki M, Yoshiya A, Kadowaki K, Ichikawa Y, Umemura M, Fujita T, Minamisawa S, Shimoda H, Mitsuru Akashi M, and Ishikawa Y: Three-Dimensional Multilayers of Smooth Muscle Cells as a New Experimental Model for Vascular Elastic Fiber Formation Studies. *Atherosclerosis* 233:590-600, 2014
 49. Okumura S, Fujita T, Cai W, Jin M, Namekata I, Mototani Y, Jin H, Ohnuki Y, Tsuneoka Y, Kurotani R, Suita K, Kawakami Y, Hamaguchi S, Abe T, Kiyonari H, Tsunematsu T, Bai Y, Suzuki S, Hidaka Y, Umemura M, Ichikawa Y, Yokoyama U, Sato M, Ishikawa F, Izumi-Nakaseko H, Adachi-Akahane S, Tanaka H, and Ishikawa Y: Epac1-dependent phospholamban phosphorylation mediates the cardiac response to stresses. *J. Clin. Invest.* 124:2785-2801, 2014
 50. Ohsawa M, Tamura K, Wakui H, Maeda A, Dejima T, Kanaoka T, Azushima K, Uneda K, Tsurumi-Ikeya Y, Kobayashi R, Matsuda M, Uchida S, Toya Y, Kobori H, Nishiyama A, Yamashita A, Ishikawa Y, and Umemura S: Deletion of the angiotensin II type 1 receptor-associated protein enhances renal sodium reabsorption and exacerbates angiotensin II-mediated hypertension. *Kid. Int.* 86:570-81, 2014
 51. Aoki R, Yokoyama U, Ichikawa Y, Taguri M, Kumagaya S, Ishiwata R, Yanai C, Fujita S, Umemura M, Fujita T, Okumura S, Sato M, Minamisawa S, Asou T, Masuda M, Iwasaki S, Nishimaki S, Seki K, Yokota S, and Ishikawa Y: Decreased serum osmolality promotes ductus arteriosus constriction. *Cardiovasc. Res.* 104:326-36, 2014
 52. Ohnuki Y, Umeki D, Mototani Y, Jin H, Cai W, Shiozawa K, Suita K, Saeki Y, Fujita T, Ishikawa Y, and Okumura S: Role of Cyclic AMP Sensor Epac1 in Masseter Muscle Hypertrophy and Myosin Heavy Chain Transition Induced by β 2-Adrenoceptor Stimulation. *J. Physiol.* 592(Pt 24):5461-75, 2014

53. Eguchi H, Umemura M, Kurotani R, Fukumura H, Sato I, Kim J-H, Hoshino Y, Lee J, Amemiya N, Sato M, Hirata K, Sigh DJ, Masuda T, Yamamoto M, Urano T, Yoshida K, Tanigaki K, Yamamoto M, Sato M, Inoue S, Aoki I and Ishikawa Y: A magnetic anti-cancer compound for magnet-guided delivery and magnetic resonance imaging. *Sci. Rep.* 5:9194, 2015
54. Kato Y, Yokoyama U, Yanai C, Ishige R, Kurotaki D, Umemura M, Fujita T, Kubota T, Okumura S, Sata M, Tamura T, and Ishikawa Y: Epac1 Deficiency Attenuated Vascular Smooth Muscle Cell Migration and Neointimal Formation. *Arterioscler. Thromb. Vasc. Biol.* 35:2617-25, 2015
55. Chetprayoon P, Matsusaki M, Yokoyama U, Tejima T, **Ishikawa Y**, and Akashi M. Three-dimensional arterial models predict the in vivo behavior of nanoparticles for drug delivery. *Angew Chem. Int. Ed. Engl.* 55(14):4461-6, 2016
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59. Ohnuki Y, Umeki D, Mototani Y, Shiozawa K, Nariyama M, Ito A, Kawamura N, Yagisawa Y, Jin H, Cai W, Suita K, Saeki Y, Fujita T, Ishikawa Y, and Okumura S: Role of phosphodiesterase 4 expression in the Epac1 signaling-dependent skeletal muscle hypertrophic action of clenbuterol. *Physiol. Rep.* 4(10). pii: e12791. doi: 10.14814/phy2.12791, 2016
60. Oda K, Umemura M, Nakakaji R, Tanaka R, Sato I, Nagasako A, Oyamada C, Baljinnam E, Katsumata M, Xie LH, Narikawa M, Yamaguchi Y, Akimoto T, Ohtake M, Fujita T, Yokoyama U, Iwatsubo K, Aihara M, and Ishikawa Y: Transient receptor potential cation 3 channel regulates melanoma proliferation and migration. *J. Physiol. Sci.* 2017 Jul;67(4):497-505. doi: 10.1007/s12576-016-0480-1. Epub 2016 Sep 9.
61. Nakamura T, Fujita T, Kishimura M, Suita K, Hidaka Ym Cai W, Umemura M, Yokoyama U, and Ishikawa Y: Vidarabine, an anti-herpes virus agent, protects against the development of heart failure with relatively mild side effects on cardiac function in canine model of pacing-induced dilated cardiomyopathy. *Circ. J.* 80(12):2496-250, 2016
62. Fujita S, Yokoyama U, Ishiwata R, Aoki R, Nagao K, Masukawa D, Umemura M, Fujita T, Iwasaki S, Nishimaki S, Seki K, Ito S, Goshima Y, Asou T, Masuda M, and Ishikawa Y: Glutamate Promotes Contraction of the Rat Ductus Arteriosus. *Circ. J.* 80(11):2388-2396, 2016
63. Kim JH, Eguchi H, Umemura M, Sato I, Yamada S, Hoshino Y, Masuda T, Aoki I, Sakurai S, Yamamoto M, and Ishikawa Y: Magnetic metal complex-conducting copolymer core-shell nanoassemblies for single-drug anticancer platform. *NPG Asia Materials* 9. e367; doi:10.1038/am.2017.29, 2017
64. Ohigashi A, Ahmed S, Afzal AR, Shigeta N, Tam-Tham H, Kanda H, Ishikawa Y, and Turin TC : Breast cancer information communicated on a public online platform: an analysis of Yahoo! Answer Japan. *J Prim. Health Care.* 2017 Jun;9(2):167-172. doi: 10.1071/HC16048.
65. Yokoyama U, Tonooka Y, Koretake R, Akimoto T, Gonda Y, Saito J, Umemura M, Fujita T, Sakuma S, Arai F, Kaneko M, and Ishikawa Y: Arterial graft with elastic layer structure grown from cells. *Sci. Rep.* 2017 Dec;7(1):140. doi: 10.1038/s41598-017-00237-1. Epub 2017 Mar 1
66. Ohtake M, Umemura M, Sato I, Akimoto T, Oda K, Nagasako A, Kim JH, Fujita T, Yokoyama U, Nakayama T, Hoshino Y, Ishiba M, Tokura S, Hara M, Muramoto T, Yamada S, Masuda T, Aoki I, Takemura Y, Murata H, Eguchi H, Kawahara N, and Ishikawa Y: Hyperthermia and chemotherapy using Fe(Salen) nanoparticles might impact glioblastoma treatment. *Sci. Rep.* 2017 Feb 20;7:42783. doi: 10.1038/srep42783
67. Kim JH, Eguchi H, and Ishikawa Y: Anticancer luminescent gold quantum clusters for in situ cancer-selective marking-imaging-targeting *Nanoscale*. DOI: 10.1039/c7nr02229h, 2017
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