

## **Kazuki Sugahara, MD, PhD**

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### **Research Update Summary – December 2020**

My goal is to develop peptide-based drug delivery systems that effectively target cancer. We mainly use tumor-specific tumor-penetrating peptides, which deliver deep into tumor tissue drugs that are chemically attached to the peptides, and even free drugs that are simply co-injected with the peptides (Sugahara et al, *Cancer Cell* 2009; *Science* 2010). One of the peptides named iRGD (clinical name CEND-1) is now in clinical trials as a co-injected enhancer of standard-of-care chemotherapy for pancreatic cancer. A phase 1 study that ended in 2020 showed that iRGD significantly potentiated co-injected chemotherapy without causing additional side effects in stage 4 pancreatic cancer patients (NCT03517176; Dean et al. *ESMO Virtual Congress 2020*, Abstract 1528P). The peptide will enter a phase 2 study in 2021.

The John Jones Fellowship awarded 2014, led to a publication in which we reported the ability of iRGD to deliver co-injected intraperitoneal chemotherapeutics selectively into peritoneal tumors by enhancing local tumor penetration (Sugahara et al, *J Control Release* 2015). Of note, this observation has allowed us to develop a novel nanosystem that probes various types of tumors such as pancreatic and breast cancer and disseminated peritoneal tumors with extremely high specificity at a level that has never been achieved before (Liu et al, *Nat Commun* 2017). Over the years, we have expanded our work to various forms of tumor-targeted immunotherapies mainly for pancreatic cancer patients. We have submitted several patent applications to this end. One of the technologies will be validated in an investigator-initiated trial in 2021.

### **Publications**

1. Tobi A, Willmore AMA, Kilk K, Braun GB, Soomets U, **Sugahara KN**, Ruoslahti E, Teesalu T. Silver nanocarriers targeted with a CendR peptide potentiate the cytotoxic activity of an anticancer drug. *Adv Therap*, 2000097 (2020).
2. Liu X, Braun GB, Qin M, Ruoslahti E, **Sugahara KN**. Tumor-specific in vivo imaging with etchable nanoprobe. *Nat Commun* 8:343 (2017).
3. Toome K, Willmore AA, Paiste P, Tobi A, **Sugahara KN**, Kirsimae K, Ruoslahti E, Braun GB, Teesalu T. Ratiometric in vivo auditioning of targeted silver nanoparticles. *Nanoscale* 9:10094-100 (2017).
4. Hunt H, Simon-Gracia L, Tobi A, Kotamraju VR, Sharma S, Nigul M, **Sugahara KN**, Ruoslahti E, Teesalu T. Targeting of p32 in peritoneal carcinomatosis with intraperitoneal linTT1 peptide-guided pro-apoptotic nanoparticles. *J Control Release* 260:142-53 (2017).
5. Ikemoto H, Lingasamy P, Anton Willmore AM, Hunt H, Kurm K, Tammik O, Scodeller P, Simon-Gracia L, Kotamraju VR, Lowy AM, **Sugahara KN**, Teesalu T. Hyaluronan-binding peptide for targeting peritoneal carcinomatosis. *Tumour Biol* 39:1010428317701628 (2017).

6. Simon-Gracia L, Hunt H, Scodeller PD, Gaitzsch J, Kotamraju VR, **Sugahara KN**, Tammik O, Ruoslahti E, Battaglia G, Teesalu T. iRGD peptide conjugation potentiates intraperitoneal tumor delivery of paclitaxel with polymersomes. *Biomaterials* 104:247-57 (2016).
7. Braun GB, **Sugahara KN**, Yu OM, Kotamraju VR, Lowy AM, Ruoslahti E, Teesalu T. Urokinase-controlled tumor penetrating peptide. *J Control Release* 232:188-95 (2016).
8. Paasonen L, Sharma S, Braun GB, Kotamraju VR, She Z, **Sugahara KN**, Yliperttula M, Wu B, Pellecchia M, Ruoslahti E, Teesalu T. New p32/gC1qR ligands for targeted tumor drug delivery. *Chembiochem* 17:570-5 (2016).
9. Willmore AM, Simon-Garcia L, Toome K, Kotamraju VR, Molder T, **Sugahara KN**, Ruoslahti E, Braun GB, Teesalu T. Targeted silver nanoparticles for ratiometric cellular phenotyping. *Nanoscale* 8:9096-101 (2016).
10. Liu X, Braun GB, Zhong H, Hall DJ, Han W, Qin M, Zhao C, Wang M, She ZG, Cao C, Sailor MJ, Stallcup WB, Ruoslahti E, **Sugahara KN**. Tumor-targeted multimodal optical imaging with versatile cadmium-free quantum dots. *Adv Funct Mater* 26:267-76 (2016).
11. **Sugahara KN**†, Scodeller P, Braun GB, de Mendoza TH, Yamazaki CM, Kluger MD, Kitayama J, Alvarez E, Howell SB, Teesalu T, Ruoslahti E, Lowy AM. A tumor-penetrating peptide enhances circulation-independent targeting of peritoneal carcinomatosis. *J Control Release* 212:59-69 (2015). (†Correspondence)
12. Hamilton AM, Aidoudi-Ahmed S, Sharma S, Kotamraju VR, Foster PJ, **Sugahara KN**, Ruoslahti E, Rutt BK. Nanoparticles coated with the tumor-penetrating peptide iRGD reduce experimental breast cancer metastasis in the brain. *J Mol Med* 93:991-1001 (2015).
13. **Sugahara KN**†, Braun GB, de Mendoza TH, Kotamraju VR, French R, Lowy AM, Teesalu T, Ruoslahti E. Tumor-penetrating iRGD peptide inhibits metastasis. *Mol Cancer Ther* 14:120-8 (2015). (†Correspondence).
14. Pang HB, Braun GB, Friman T, Aza-Blanc P, Ruidiaz M, **Sugahara KN**, Teesalu T, Ruoslahti E. An endocytosis pathway initiated through neuropilin-1 and regulated by nutrient availability. *Nat Commun* 5:4904 (2014).
15. Braun GB, Friman T, Pang HB, Pallaoro A, de Mendoza TH, Willmore AMA, Kotamraju VR, **Sugahara KN**, Reich NO, Teesalu T, Ruoslahti E. Etchable plasmonic nanoparticle probes for cell biology. *Nat Mater* 13:904-11 (2014).

## Honors

Idea Award with Special Focus, Department of Defense (USA, 2020)

Blakemore Prize for Resident Research, Department of Surgery, Columbia University (USA, 2019)

Finalist, Poster Competition, Society of Surgical Oncology Annual Meeting (USA, 2019)

Blakemore Award, 1st Annual Research Symposium, Columbia University (USA, 2017)

2nd Place, Annual Research Competition, Department of Surgery, Columbia University (USA, 2016)

Finalist, Poster Competition, Society of Surgical Oncology Annual Meeting (USA, 2015)

John Jones Surgical Society Fellowship Award, Columbia University (USA, 2014)