第６回 iCONM 学術セミナーのご案内

平素から大変お世話になっております。

ナノ医療イノベーションセンター（iCONM）では、プロジェクト COINS の終了に伴い、これまで開催してきました「COINS セミナー」を「iCONM 学術セミナー」と改称し、引き続き開催させて頂くこととなりました。弊センターの公開イベントとして、他に「市民公開講座」を開催しておりますが、「iCONM 学術セミナー」は、より専門的で学術的な内容のものと位置付けております。

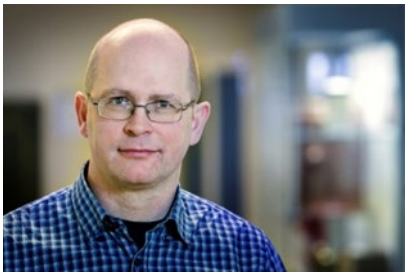
第６回目は、アイスランド大学より Már Másson 教授をお迎えし、以下に記す要領で 11/30 午前１０時より開催致します。Másson 教授の専門は医薬品化学で、特に甲殻類の殻から取れるキトサンを中心とした創薬研究を行っています。今回の講演では、Photochemical Internalization (PCI) 技術を用いたがん治療がテーマとなります。PCI は、両親媒性の光増感剤を用いて細胞内へ薬剤を送達する技術で、光をトリガーとして部位特異的に治療が行えるという点で注目されています。オンラインでの開催となりますので、事前登録によりアクセスに必要な URL を入手頂けますようお願い致します。今後ともホットな内容にフォーカスを充てた企画を立てていく所存ですので、引き続きよろしくお願い致します。

2022 年 11 月 18 日
ナノ医療イノベーションセンター
イノベーション推進チーム

記

日時：2022 年 11 月 30 日　9 時 45 分開場　10 時 00 分開演
場所：ZOOM によるオンライン開催
演題：Selective synthesis of chitosan nano-conjugates for photochemical internalization cancer therapy
講師：Dr. Már Másson
Professor Medicinal Chemistry, Faculty of Pharmaceutical Sciences, School of Health Sciences, University of Iceland
言語：英語
事前申込み：
https://iconm.kawasaki-net.ne.jp/form/academic-seminar6/

講師略歴：



Már Másson, completed BS in chemistry from the University of Iceland in 1987, Cand. Scient (MS) organic chemistry, Copenhagen University, Denmark in 1990 and Doctor of Engineering – Biotechnology

from Tokyo Institute of Technology, Japan, in 1995.
He became Post-Doc at the University of Iceland Department of Pharmacy in 1995, Assoc. Prof. in medicinal chemistry in 1998 and since 2005 he has been a Professor in Medicinal Chemistry at the University of Iceland, Faculty of Pharmaceutical Sciences.
The research group headed by Már Másson is mainly focused on the synthesis and investigation of chitosan derivatives. The group developed TBDMS protection strategy for chitosan that can be utilized for chemoselective and highly controlled synthesis of chitosan derivatives. The applications that have been investigated are: chitosan derivatives as antimicrobial agents, chitosan derivatives as permeation enhancers affecting tight junctions in the pulmonary epithelium, chitosan nanocarriers for photochemical internalization, and chitosan derivatives as coatings for application in regenerative medicine. Már Másson also collaborates with engineers and mathematicians in Iceland focusing on developing a numerical framework for modeling drug delivery systems including transdermal and ophthalmic drug delivery systems and and bioelectronics based on chitosan.

講演要旨：

Photochemical internalization (PCI) is a novel technology, which utilizes selected photosensitizers (PS) in combination with light excitation, to induce the release of endocytosed hydrophilic drugs so they can reach their target before being degraded in lysosomes. This therapy has been shown to be effective in the clinic but the efficiency could potentially be further improved with polymeric nanocarriers. These would allow for tumor-selective accumulation due to the enhanced permeation and retention (EPR) effect. The aim of the current study was to develop the synthesis and investigate nanoconjugates, that were composed of cationic chitosan derivatives with covalently linked highly lipophilic photosensitizers. TBDMS-protected chitosan was utilized for the efficient synthesis of highly substituted nanoconjugates. The proof-of-concept study was done with tetraphenylporphyrin (TPP) as the photosensitizer [1]. The nanoconjugate structure and degree of substitution was determined by 1-H and solid-state NMR. Physiochemical characteristics were also investigated by fluorescence, dynamic light scattering, and size exclusion chromatography. The nano-conjugates formed nanoparticle-like structures with an average size of nanoparticles in the range of 100-300 nm. The TPP nanoconjugates were effective for PCI-mediated gene delivery in a human colon carcinoma cell line.

The more challenging tetraphenylchlorin (TPC) conjugates were also synthesized

[2]. These offer the advantage of possible activation and longer wavelengths (650 nm) and are therefore suitable for *in vivo* use. A dynamic light scattering (DLS) study confirmed the formation of nanoparticles with a 140–200 nm diameter. These nanoconjugates were taken up and localized in the endocytic vesicles of HCT116/LUC human colon carcinoma cells, and upon illumination, they substantially enhanced plasmid DNA transfection. The nanoconjugates were also evaluated in preliminary in vivo experiments in tumor-bearing mice, showing that the nanoconjugates could induce strong photodynamic therapy (PDT) and also PCI effects in treatment with bleomycin.

The TPC conjugates were also used to develop biodegradable polymeric nanoparticles (NPs) containing the cytostatic drugs mertansine (MRT) or cabazitaxel (CBZ) [3]. The TPC–CS NPs had high loading capacity and strong drug retention due to π–π stacking interactions between the drugs and the aromatic photosensitizer groups of the polymers. The TPC–CS NPs loaded with MRT or CBZ displayed higher cytotoxicity than the free form of these drugs in the breast cancer cell lines MDA-MB-231 and MDA-MB-468. Biodistribution studies in mice showed that most of the TPC–CS NPs accumulated in the liver and lungs, but they were also found to be localized in tumors derived from HCT-116 cells. These data suggest that the drug-loaded TPC–CS NPs have potential in combinatory anticancer therapy and as contrast agents.

[1] Vivek S. Gaware, Monika Håkerud , Kristján Leósson, Sigríður Jónsdóttir, Anders Høgset, Kristian Berg, Már Másson (2013). Tetraphenylporphyrin Tethered Chitosan Based Carriers for Photochemical Transfection. *Journal of Medicinal Chemistry* **56**, 807−819 (dx.doi.org/10.1021/jm301270r)

[2] Vivek S. Gaware, Monika Håkerud, Asta Juzeniene, Anders Høgset, Kristian Berg, Már Másson. (2017) Endosome Targeting meso-Tetraphenylchlorin-Chitosan Nano-Conjugates for Photochemical Internalization *Biomacromolecules* **18** (4), 1108-1126 (https://doi.org/10.1021/acs.biomac.6b01670)

[3] Abhilash D. Pandya, Anders Øverbye, Priyanka Sahariah, Vivek S. Gaware, Håkon Høgset, Màr Masson, Anders Høgset, Gunhild M. Mælandsmo, Tore Skotland, Kirsten Sandvig, and Tore-Geir Iversen*. (2020) Drug-loaded Photosensitizer-Chitosan Conjugate Nanoparticles for Combinatorial chemo- and photodynamic therapy in Breast Cancer Cells. – *Biomacromolecules* **19** (9) 3649-3658 (https://doi.org/10.1021/acs.biomac.0c00061)