Tracing proliferating potential of lung tumours by [^{11}C]Nicotinamide

Robert Bielik[1], Gavin Brown[1]], Dmitry Soloviev[2] , David Y. Lewis [1,2]

(1) Cancer Research UK Scotland Institute, Glasgow, UK
(2) School of Cancer Sciences, University of Glasgow, Glasgow, UK

Many tumours rely on aerobic glycolysis, known as the Warburg effect, to satisfy energy needs and sustain rapid proliferation [1]. High demands of glucose in tumours can be measured by [^{18}F[fluorodeoxyglucose, [^{18}F]FDG, positron emission tomography (PET). Nicotinamide adenine dinucleotide (NAD) is a coenzyme involved in redox reactions in many metabolic pathways, including glycolysis. To maintain the high rates of glycolysis and proliferation, tumours need increased NAD^+ levels and use nicotinamide for the upregulated NAD^+ salvage pathway that is the main source of NAD^+ in proliferative cancer cells [2]. Herein, we show an improved synthesis method of [^{11}C]Nicotinamide, [^{11}C]NAM, and studied the uptake of [^{11}C]NAM and [^{18}F]FDG to measure proliferating capacity in a lung cancer model.

[Carboxyl-^{11}C]nicotinamide was synthesized by a one-pot radiolabeling method [3] on the SYNTHRA synthesizer (Synthra GmbH, Germany) (see Figure 1A). We used a $Kras^{G12D/+}$ genetically engineered mouse model of lung cancer and evaluated the uptake of [^{11}C]nicotinamide and [^{18}F]FDG with dual-tracer sequential imaging protocol (see Figure 1B) using a NanoScan PET/MRI scanner (Mediso Medical Imaging Systems, Hungary).

We obtained [carboxyl-^{11}C]nicotinamide in a radiochemical yield of 15 ± 5 %, volumic activity of 50 ± 10 MBq/ml, and radiochemical purity was > 99 %. We optimized the imaging protocol and found the uptake of [^{11}C]nicotinamide co-localized with the uptake of [^{18}F]FDG in the $Kras^{G12D/+}$ model of lung cancer as shown in Figure 1C suggesting the higher NAM uptake was associated with high NAD^+ production in highly proliferating tumours.

We demonstrated that metabolic PET/MRI imaging with [^{11}C]NAM can complement [^{18}F]FDG PET and be useful for probing proliferative potential in lung cancer. This method could be translated and applied in clinical practice to enable visualization of NAD^+ metabolism in lung tumours and targeted therapeutically.

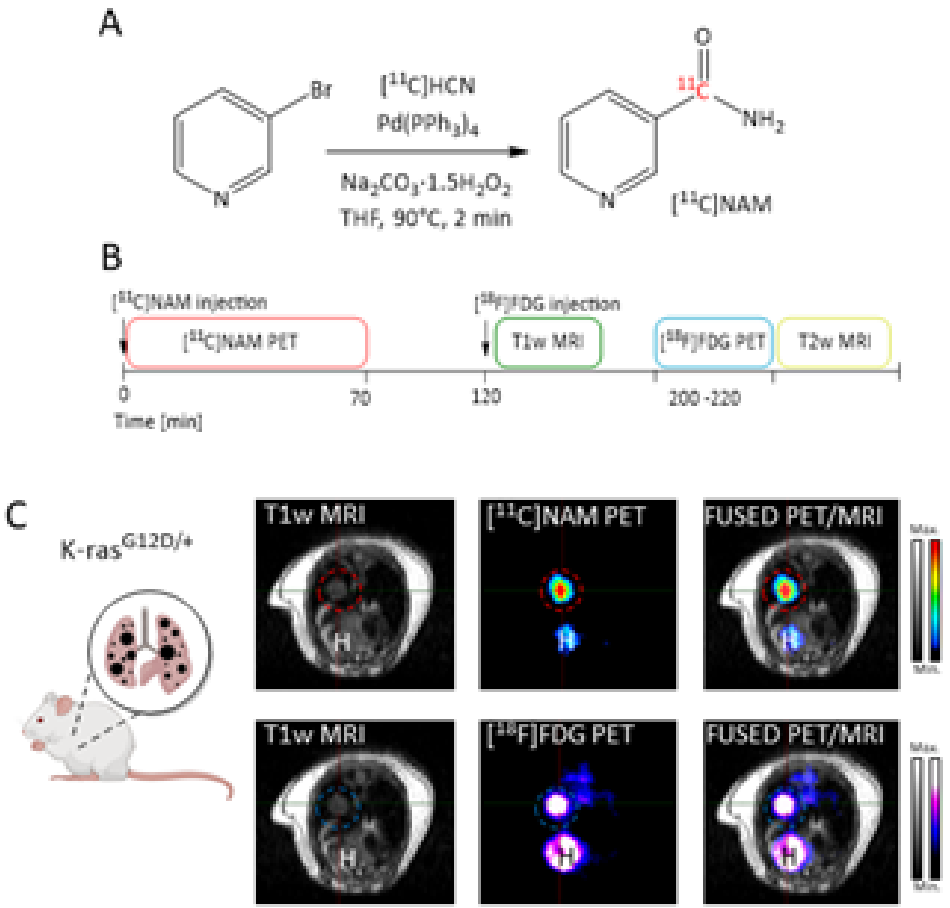

Figure. 1 Tracing proliferating potential of lung tumours by [^{11}C]Nicotinamide. (A) Synthesis of [carboxyl-^{11}C]nicotinamide from 3-bromopyridine and hydrogen [^{11}C]cyanide catalysed by palladium. (B) Dual-tracer sequential imaging protocol with [^{11}C]nicotinamide and [^{18}F]FDG. [^{11}C]NAM PET was acquired 0-70 min post-injection of 35±5 MBq/mouse and [^{18}F]FDG PET was acquired 80-100 min post-injection of 10±2 MBq/mouse with anatomical T1 and T2-weighted MRI. (C) Transversal T1-weighted MRI and PET images for [^{11}C]NAM (tumour circled in red) at 30 min p.i. and [^{18}F]FDG (tumour circled in blue) at 90 min p.i. in a K-ras$^{G12D/+}$ lung cancer model. H indicates a PET signal from the heart.

References:

(1) Vander Heiden MG, Cantley LC, Thompson CB. *Understanding the Warburg effect: the metabolic requirements of cell proliferation.* Science. 2009 May 22;324(5930):1029-33. doi: 10.1126/science.

(2) Navas LE, Carnero A. *NAD+ metabolism, stemness, the immune response, and cancer.* Signal Transduct Target Ther. 2021 Jan 1;6(1):2. doi: 10.1038/s41392-020-00354-w.

(3) Makaravage KJ, Shao X, Brooks AF, Yang L, Sanford MS, Scott PJH. *Copper(II)-Mediated [^{11}C]Cyanation of Arylboronic Acids and Arylstannanes.* Org Lett. 2018 Mar 16;**20**(6):1530-1533. doi: 10.1021/acs.orglett.8b00242.