Hypoxia-selective copper radiopharmaceuticals

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Essay (921 words)

Hypoxia is a pathological condition where tissue oxygen concentration ($pO_2$) decreases to less than 10% of normal levels and is associated with heart disease, stroke and various cancers. Tumour hypoxia presents a major problem in the clinical management of cancer because low tissue oxygenation confers resistance to both chemotherapy and ionising radiation and reduces patient survival rates. Therefore, the ability to image and quantify hypoxia non-invasively in vivo using techniques such as positron emission tomography (PET) would facilitate early diagnosis and treatment of cancer, and improve patient prognosis for disease-free survival. My post-graduate research focused on the rational design of metal-based radiopharmaceuticals for use as in vivo imaging and radiotherapeutic agents targeting hypoxia.

The central hypothesis of my thesis was that: An integrated approach using synthetic, computational and spectroelectrochemical methods can elucidate the mechanism of hypoxia-selectivity, identify key structure-activity relations and facilitate the rational design of new copper-based radiopharmaceuticals for PET imaging.

Copper bis(thiosemicarbazonato) complexes have been investigated for over 50 years as anti-tumour agents. Over the last decade intense research efforts have lead to the development of one complex, [CuIIATSM], as a hypoxia-selective radiopharmaceutical for in vivo PET imaging and potential radiotherapy of tumours (Figure 1).[1] Following successful preclinical trials, the United States Food and Drug Administration (FDA) recently approved the copper-64 radiolabelled complex, [64CuIIATSM], for use in multi-centre trials imaging patients with cervical cancer.[2] Further clinical trials are planned in Europe and the US.

The fluorine-18 radiolabelled compound, [18F]-fluoro-misonidazole ([18F]-FMISO) is the most widely used tracer in the clinic for in vivo PET imaging of tumour hypoxia. Many studies have demonstrated that [18F]-FMISO uptake is indicative of tissue oxygenation and is selective for tissues with $pO_2 < 3$ mmHg. However, the unfavourable pharmacokinetics and imaging characteristics of [18F]-FMISO have limited its wider application in clinical oncology. These limitations include low tumour-to-background (T/B) contrast ratios (typically <1.2 for blood and muscle) and slow clearance from background tissue. Optimal contrast requires a 2 hour delay before image acquisition, during which time the $^{18}$F ($t_{1/2} = 109.7$ min.) has decayed by one half-life, which reduces the signal-to-noise. In comparison [CuIIATSM] radiolabeled with $^{60}$Cu ($t_{1/2} = 23.7$ min.) or $^{64}$Cu ($t_{1/2} = 12.7$ h) can delineate tumour hypoxia in <1 h with T/B contrast ratios typically >2.0 and uptake has been shown to be predictive of patient response to therapy.[1]

Despite the clinical success of [CuIIATSM] and prior to the commencement of my post-graduate studies, precise details on the mechanism of cellular metabolism and hypoxia-selective structure-activity relations remained unknown. This uncertainty represents a major problem to both clinicians seeking to use [CuIIATSM] for quantitative in vivo measurements of tumour hypoxia, and to chemists working to develop second-
generation copper-based radiopharmaceuticals with improved tumour selectivity. My studies addressed important questions pertaining to the mechanism of hypoxia-selectivity and went further by using the knowledge gained in the rational design of new second-generation imaging agents (Figure 1A – C). Density functional theory (DFT) calculations were used to probe the electronic structure of the bis(thiosemicarbazone) core, and new methods for calculating absolute redox potentials and pK_a values were developed.[3] Predictions from the DFT calculations were subsequently validated by detailed spectroelectrochemical studies,[4] and the intimate combination of theory and experiment facilitated the proposal of a new mechanism of hypoxia-selectivity.[5] Understanding the molecular origins of hypoxia-selectivity proved invaluable in the rational design of a new class of functionalised copper complexes.[6-8] A new glucose-functionalised copper-64 complex, [64CuIIATSM-Glc] has recently been evaluated \textit{in vivo} and was found to exhibit increased tumour uptake and greatly improved image contrast.[9, 10]

Translating a radiolabelled compound from the laboratory to the clinic is a challenging process. The ideal system allows for rapid synthesis of the radiopharmaceutical with high yield, purity and as a sterile, pyrogen-
free product. In order to facilitate translation of our new copper-based agents to the clinic we developed an elegant one-step solid-phase procedure which allows for automated preparation of high purity and high specific-activity copper-based radiopharmaceuticals by transmetallation from their zinc analogues.[10] The protocol has a wide scope and has also been successfully applied for the production of technetium-99m and gallium-68 complexes. Plans for further preclinical and clinical trials are underway and many of the new complexes will be evaluated in vivo during 2009/10.

Development of new radiopharmaceuticals is a highly interdisciplinary field of research in which chemistry plays a pivotal role. The two main achievements from my post-graduate studies include elucidation of the mechanistic details of hypoxia-selectivity of copper bis(thiosemicarbazonato) complexes and the design of new synthetic and computational methods for evaluating the potential of new copper-based compounds to be use as radiopharmaceuticals. Work from my thesis has been published in over 15 peer-reviewed articles including prestigious journals such as The Journal of Nuclear Medicine, Angewandte Chemie, Chemistry – A European Journal, Inorganic Chemistry and Dalton Transactions and in combination with efforts from other groups around the world, will eventually lead to the translation of a potent diagnostic radiopharmaceutical for imaging of tumour hypoxia in the clinic.

References