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## ORAL PRESENTATIONS

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## **I-123 BASED DEVELOPMENT PROGRAM AT MDS NORDION**

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Ultra-pure iodine-123 (>99.8% radionuclide purity) has been produced by the irradiation of enriched xenon-124 (>99.8%) on external beam lines of CP-42 and TR-30 cyclotrons. Typically, an incident proton energy of 24-30 MeV has resulted in a yield of 6.6 mCi/uAh at the end of processing (end of bombardment + 9h). The largest quantity of iodine-123 produced on a single run has been 12 Ci. The availability of large quantities of ultra-pure I-123 and reliable production four to five times per week has led to a vibrant radiopharmaceutical program based on I-123. Currently, a number of pharmaceuticals have been licensed in Canada or are undergoing clinical trials in the United States. MDS Nordion has state of the art facilities such as Class 100 Isolators in Class 10,000 Clean Rooms for aseptic filling operations and has developed expertise in Ci scale labeling operations.

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## **A New Encapsulated Target System for Isotope Production**

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"Solid target" Systems are conventionally used to produce radioisotopes from target materials that can be electroplated onto a water-cooled surface. Gases can be irradiated within sealed chambers. However, other materials such as metals with a low melting point, powders, etc. are conventionally more difficult to irradiate in a general purpose target system due to their specific characteristics. To get around this problem, an encapsulated target system has been designed and a prototype target, shown in Fig. 1, was built and tested.

The main characteristics of this system are its similarity to the existing solid target system. The targets are transferred between the hot cells and the target station using the existing pneumatic transfer system and insertion of the targets into the irradiation chamber uses a similar manipulation system that also provides water connections for cooling. The main differences are the target and water cooling mechanism within the target body. Figure 1 shows the direction of water flow, which is directed onto the center of the target, spreads out radially, and finally returns concentrically outside of the incoming water line. A computer simulation of the effectiveness of this method of cooling was developed and used to optimize the design parameters of the target structure.

A prototype target was built and, using a suitable adapter, was tested on one of the existing solid target stations. Special embedded and electroplated thermocouples on the target surface were used to measure the temperature during beam irradiation. The results were very encouraging since maximum temperatures did not exceed 1000C at 200 uA (30 MeV).

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## **THE MEDICAL ISOTOPE PROJECT: MAPLE 1 & 2**

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MDS Nordion is building two specialized MAPLE reactors (10 mega watts) and a processing facility dedicated to medical isotope production at Atomic Energy of Canada's (AECL) Chalk River Laboratories site.

The planned facility will produce molybdenum 99, which decays into technetium 99m - the isotope most widely used in hospitals and clinics to diagnose many illnesses. More than 50,000 procedures are carried out around the world each day to diagnose cancer, heart disease, as well as to detect other problems in the brain, heart, lungs, liver, thyroid, kidneys and bone. Nuclear Medicine can continue to rely on MDS Nordion produced radioisotopes.

The facilities will also produce xenon-133, iodine-131 and iodine-125. MAPLE 1 will be the main isotope producer. MAPLE 2 will provide alternate production during maintenance shut downs of the primary reactor. Each reactor is housed in a separate building. The MDS Nordion MAPLE reactors will provide a secure supply of critical medical isotopes well into the next century.

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### **Heavy Water Production Through Catalytic Exchange**

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Earlier this year AECL had committed to build a prototype CIRCE (Combined Industrial Reforming and Catalytic Exchange) plant for the production of heavy water (1Mg per year). This new process, which extracts deuterium from a steam-reformed hydrogen source will be constructed in the Province of Ontario in conjunction with a new steam methane reformer being built by an industrial partner. This plant would incorporate the BHW (Bithermal heavy water) process and the CECE (Combined Electrolysis and Catalytic Exchange) process in its second and third stages, respectively. Commissioning of a pilot-scale unit to demonstrate the use of the CECE process for upgrading and detritiation of heavy water is currently in progress at the Chalk River Laboratories.

The heart of the above liquid phase catalytic exchange (LPCE) processes is the "wetproofed catalyst" developed at AECL for the exchange of hydrogen isotopes between hydrogen gas and liquid water. Highly active structured catalytic modules that incorporate hydrophobic catalytic layers and hydrophilic mass-transfer layers have been developed. The isotope-exchange reaction takes place on the hydrophobic catalytic layers while the isotope transfer between water vapour and liquid water occurs on the hydrophilic layers. Optimization of the performance of these two processes has been a challenging task due to the fact that they require opposing surface properties.

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### **In-Target Chemistry: A Review of the Production of Precursors for PET Radiopharmaceuticals**

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The technique of positron emission tomography (PET) for in-vivo physiologic investigations is predicated on the ability to synthesize radiopharmaceutical tracers unperturbed in action by the addition of a radionuclide. The most favourable radionuclides for PET to date are  $^{11}\text{C}$  and  $^{18}\text{F}$  with half-lives of 20 min and 110 min respectively. These half-lives, in turn, dictate a facile and speedy synthesis route for the desired tracer. The selection of suitable target conditions and constituents can aid in the achievement of fast and facile syntheses of a number of radiopharmaceuticals.

Methylation reactions with  $^{11}\text{CH}_3\text{I}$  are widely used for the synthesis of tracers employed in neurologic studies. Methyl iodide has generally been synthesized from the target product  $^{11}\text{CO}_2$ , produced via the nuclear reaction  $^{14}\text{N}(p,a)^{11}\text{C}$  where a cyclotron is used to bombard a pressurized gas cell of high purity natural abundance  $^{14}\text{N}_2$  with trace amounts of  $\text{O}_2$ . The in-target conditions are optimized to favour the production of  $^{11}\text{CO}_2$ . Recently an alternate method of synthesizing  $^{11}\text{CH}_3\text{I}$  was developed which employs as a starting point  $^{11}\text{CH}_4$ . This methane can be produced in one of two ways, by the in-target production of  $\text{CO}_2$ , as before, followed by the catalytic conversion of  $\text{CO}_2$  to  $\text{CH}_4$ , or alternately, by the in-target production of  $^{11}\text{CH}_4$ . This second method has the advantage of being faster and the potential for a higher specific activity. In this case high purity natural abundance  $^{14}\text{N}_2$  is mixed with high purity  $\text{H}_2$  to optimize the in-target production of  $^{11}\text{CH}_4$ .

$^{18}\text{F}$  is another favoured positron emitter for its ability to be substituted in place of a hydrogen atom with, in some cases, minimal affect on the function of the molecule. The synthesis of  $^{18}\text{F}$ -FDG, as the most widely used PET compound, can be conducted from target products. In both cases the target material is enriched  $^{18}\text{O}$ ,  $^{18}\text{O}\text{-H}_2\text{O}$  for  $^{18}\text{F}$ , and  $^{18}\text{O}_2$  for  $^{18}\text{F}\text{-F}_2$  with the nuclear reaction  $^{18}\text{O}(p,n)^{18}\text{F}$  being employed. The production of  $^{18}\text{F}$  is the simple irradiation of a small water sample with the product emerging as aqueous  $\text{H}^{18}\text{F}$ . The production of  $^{18}\text{F}\text{-F}_2$  entails a two-step irradiation process, whereby the first irradiation is the production of  $^{18}\text{F}$  in a high pressure gas cell. The  $^{18}\text{O}_2$  is then cryogenically recovered in a small, liquid nitrogen cooled vessel, and the target refilled with a small amount of natural abundance  $\text{F}_2$  mixed in an inert gas. A second irradiation drives an isotopic exchange between the  $^{18}\text{F}\text{-F}_2$  and the  $^{19}\text{F}$  on the target walls resulting in  $^{18}\text{F}\text{-}^{19}\text{F}$  among the larger concentration  $^{19}\text{F}_2$  in the target gas.

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### **FDG-PET TO MONITOR EARLY TUMOR RESPONSE IN MICE AFTER PHOTODYNAMIC THERAPY**

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The aim of this study was to investigate the use of [ $^{18}\text{F}$ ]fluoro-2-deoxy-D-glucose (FDG) and an animal PET camera to assess early tumor response in mice following photodynamic therapy (PDT). PDT consists of intravenous administration of a photosensitizer which accumulates preferentially in tumor tissue, followed by local illumination of the tumor with red light. Two different photosensitizer were used, Photofrin $\text{B}$  (P11) which is approved for clinical use and a second-generation drug, disulfonated aluminum phthalocyanine (AIPcS). These drugs have previously been shown to induce tumor necrosis via different action mechanisms, i.e. initial vascular stasis (PII) or direct tumor cell kill (AIPcS). FDG-PET was used to follow both perfusion and metabolic activity in the tumor tissue.

The study was performed using a mouse model implanted with two contralateral murine mammary tumors (5 mm diameter x 2.5 mm thickness) on the back. Only one tumor was subjected to PDT while the other served as control. A total of 13 mice were studied without illumination and at 30 minutes and 2 hours after PII-PDT or AIPcS-PDT. Dynamic PET imaging of the mice placed in pair in a prostrate position parallel to the transaxial planes of the Sherbrooke animal PET scanner was performed following a bolus injection of 300  $\mu\text{Ci}$  of FDG. Blood samples were collected concurrently from one mouse for each study using an automated microvolumetric blood sampler.

Analysis of the tumor time-activity curves showed that: 1) Scans during the first 3 minutes provide a good estimate of tumor perfusion, as confirmed by the FDG activity in the blood samples; 2) the tumor FDG-uptake after 15 minutes is a direct measurement of tumor metabolism clearly demonstrating the relative efficiency of the two PDT drugs. We conclude that the slope of the time-activity curve in the interval 200-1000 seconds after FDG injection is an appropriate indicator of the different mechanisms of tumor necrosis through indirect vascular stasis (PII) or direct cell kill (AIPcS). This pilot study confirms the feasibility of dynamic in vivo PET imaging in mice for assessing early tumor response to an experimental treatment protocol.

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## MEASUREMENTS OF BRAIN SEROTONIN SYNTHESIS WITH LABELLED $\alpha$ -METHYL-L-TRYPTOPHAN

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We have labelled methyl-L-tryptophan [ $\alpha$ -MTrp] with  $^{14}\text{C}$ ,  $^{11}\text{C}$  and  $^3\text{H}$  in the  $\alpha$ -methyl position. The labelling was done by reacting an anion, created at 700 C from a suitable starting material [e.g. dimethyl 8-acetyl-(2S, 3aR, 8aS)-(+)-hexahydropyrrolo[2,3-b] indole-1,2-dicarboxyl ate] with lithium disopropylamide (LDA) in tetrahydrofuran, with appropriately labelled methyl iodide. In the synthesis of  $^{11}\text{C}$ -labelled  $\alpha$ -MTrp, methyl iodide was carried into the reaction mixture with a stream of nitrogen. In the synthesis of  $^{14}\text{C}$  and  $^3\text{H}$  labelled  $\alpha$ -MTrp methyl iodide as liquid was transferred under reduced pressure from the reservoir containing methyl iodide into solution containing anion.  $^{11}\text{C}$ -labelled  $\alpha$ -MTrp was used for studies of serotonin synthesis

in dog and human brains in conjunction with positron emission tomography (PET). In rats we used tracer to study the influence of a hypothalamic lesion with 5,7-dihydroxytryptamine and different pharmacological treatment (e.g. fluoxetine, fenfluramine, reserpine) on the serotonin synthesis. In dog and human brains the influence of the plasma tryptophan on the brain serotonin synthesis was evaluated. Results of these investigations will be presented to exemplify the utility of labelled  $\alpha$ -MTTrp in biological studies. Research was supported by the MRC and NIH grants.

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## SHORT-LIVED RADIONUCLIDE-LABELED RADIOPHARMACEUTICALS FOR IMAGING WITH PET

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Positron emission tomography (PET) is an imaging technique that measures non-invasively and with high resolution (5-10 mm) the concentration of a radioligand labeled with a positron-emitting isotope in the living human. The main advantage of PET is the possibility to label an organic molecule of biochemical interest with a positron-emitting isotope of several elements, such as  $^{15}\text{O}$ ,  $^{13}\text{N}$ ,  $^{11}\text{C}$  and  $^{18}\text{F}$ . These short-lived radionuclides are produced with a cyclotron. The external analysis of the kinetic fate of the radioisotope-labeled molecule within the biological system is performed using a positron camera. Clinical PET imaging is mainly performed in oncology, cardiology and neurosciences.

Due to the very short half-life of  $\sim$  (2.07 min), it is used in serial studies (e.g. blood flow with [ $^{15}\text{O}$ ]H<sub>2</sub>O) in the same individual at short time intervals. Depending on the cyclotron,  $^{15}\text{O}$  can be produced by different nuclear reactions, such as the low-energy nuclear reaction  $^{15}\text{N}(p,n)^{15}\text{O}$ , or the medium-energy  $^{14}\text{N}(d,n)^{15}\text{O}$  reaction. [ $^{13}\text{N}$ ]Ammonia ( $^{13}\text{N}$ , T<sub>1/2</sub>: 9.96 min) is mostly used as a myocardial blood flow imaging agent.  $^{13}\text{N}$  can be prepared by the nuclear reaction  $^{16}\text{O}(p,a)^{13}\text{N}$ . The longer half-life of  $^{11}\text{C}$  (20.4 min) and especially  $^{18}\text{F}$  (109.7 min) allows more complex or multistep organic synthesis. It also permits extending scanning periods to 90-min maximum post-injection with  $^{11}\text{C}$ -labeled derivatives, and to 6 h with  $^{18}\text{F}$ . As compared to other positron-emitting isotopes, the emitted positron from  $^{18}\text{F}$  has a lower energy (maximum 0.635 MeV) and thus "travels" a shorter range  $\sim$  mm in water), increasing the resolution in the PET images. In addition, the longer half-life of  $^{18}\text{F}$  affords the capability of shipping  $^{18}\text{F}$ -labeled derivatives to other sites at moderate distances from the site of production. Both  $^{18}\text{F}$  and  $^{11}\text{C}$  radionuclides can be produced in high specific activities, which is very important for their use in tracer doses in receptor imaging PET studies.

Carbon-11 is produced by the nuclear reaction  $^{14}\text{N}(p,a)^{11}\text{C}$ .  $^{11}\text{C}\text{O}_2$  is the most widely used precursor form of carbon-11 for radiotracer synthesis, and is produced in the presence of small quantities ( $\sim$ 1%) of  $\text{O}_2$  in the target. It can be converted to a variety of  $^{11}\text{C}$  precursors including  $^{11}\text{C}\text{H}_3\text{I}$ , which is used to label numerous radiotracers in neuroreceptor studies. For example, the D1 antagonist [ $^{11}\text{C}$ ]SCH 23390, D1 agonist [ $^{11}\text{C}$ ]SKF 82957, D2 antagonist [ $^{11}\text{C}$ ]raclopride and the dopamine transporter blocker [ $^{11}\text{C}$ ]RTI 32 are routinely prepared here in Toronto, using

$^{11}\text{C}$  and the desmethyl precursors.

Both electrophilic and nucleophilic forms of fluorine-18 can be prepared for radiochemical synthesis. When the specific activity is not a concern, e.g. 2-deoxy-2- $^{18}\text{F}$ fluoro-D-glucose ( $^{18}\text{F}$ FDG) or L- $^{18}\text{F}$ dopa (due to the abundance of the corresponding unlabeled derivative), electrophilic reactions with  $^{18}\text{F}_2$  can be utilized. Fluorine-18 is usually produced by the nuclear reaction  $^{22}\text{Ne}(d,a)^{18}\text{F}$ .  $^{18}\text{F}$ FDG can also be prepared by nucleophilic  $^{18}\text{F}$ -fluoride substitution. For the development of high specific activity  $^{18}\text{F}$ -labeled radiopharmaceuticals using nucleophilic reactions with the  $^{18}\text{F}$ -fluoride ion, the nuclear reaction of choice is  $^{18}\text{O}(p,n)^{18}\text{F}$  using enriched  $^{18}\text{O}$ -water in a small volume silver target. An example of the latter reaction is employed here in the radiosynthesis of  $^{18}\text{F}$ setoperone, from 1SF and the nitro-derivative precursor of setoperone, for imaging 5-HT<sub>2A</sub> receptors with PET.

### USING $^{11}\text{C}/^{14}\text{C}$ INCOMING GROUP AND SECONDARY ALPHA DEUTERIUM KINETIC ISOTOPE EFFECTS TO SHOW HOW CHANGING THE LEAVING GROUP ALTERS TRANSITION STATE STRUCTURE IN AN $\text{S}_{\text{N}}2$ REACTION

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The  $^{11}\text{C}/^{14}\text{C}$  incoming group and secondary alpha deuterium KIEs and Hammett  $\rho$  value found by changing the substituent in the leaving group of the  $\text{S}_{\text{N}}2$  reactions between meta-chloro-benzyl-para-substituted benzenesulfonates and cyanide ion in 0.5% aqueous acetonitrile at 0°C

<i>Para</i> Substituent	$k_{11}/k_{14}$	$(k_{\text{H}}/k_{\text{D}})_a$
$\text{CH}_3\text{O}$	-	1.025±0.008
$\text{CH}_3$	1.0119 ± 0.0010	1.028 ± 0.005
H	1.0111 ± 0.0020	1.012 ± 0.008
Cl	1.0096 ± 0.0005	1.009 ± 0.012

suggest that these reactions occur via an unsymmetrical, product-like transition state. Changing to a better leaving group leads to a transition state with a slightly shorter nucleophile - alpha carbon bond and a longer alpha carbon - leaving group bond in accordance with the "Bond Strength Hypothesis" for  $\text{S}_{\text{N}}2$  reactions.

### DEVELOPMENT OF NEW MICROWAVE ENHANCED DEUTERIATION AND TRITIATION

## PROCEDURES

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Deuterium ( $^2\text{H}$ ) and tritium ( $^3\text{H}$ ) labelled compounds are widely used in the physical and life sciences <sup>1</sup>. Whilst most of the labelling methods can be used for both  $^2\text{H}$  and  $^3\text{H}$  there are important differences, not least the fact that tritium is radioactive. Consequently with increasingly demanding legislation it is important to devise new, more selective methods which lead to excellent incorporation and keep the radioactive waste down to a minimum. This has been our thrust of late whilst carrying out preliminary deuteration studies.

Only 12 years have elapsed since two important papers<sup>2,3</sup> appeared in which the potential use of microwaves in synthetic organic chemistry was explored. In the meantime the area has seen tremendous growth<sup>4</sup> but as far as labelling compounds with isotopes is concerned only the radiopharmaceutical area, involving short-lived positron emitters such as  $^{11}\text{C}$  and  $^{18}\text{F}$  has been explored.<sup>5,6</sup>

In general deuteration and tritiation procedures fall into the following categories:

- | hydrogen isotope exchange reactions
- | reduction reactions
- | hydrogenation reactions
- | dehalogenation reactions
- | methylation reactions

We have now found that all of the reactions (apart from the last) can benefit from the use of microwaves. In this talk we shall concentrate on the first two of the above reactions namely (a) acid-catalysed hydrogen isotope exchange reactions and (b) borohydride reductions of carbonyl compounds.

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### Stable Isotope-Aided NMR Studies of Protein-Peptide Complexes

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The interactions and binding of small peptides to their cognate protein receptors have been probed using isotopically labeled peptides and multi-dimensional solution state NMR techniques. We have studied the complexes formed between several different peptides and their protein receptors using peptides synthesized using stable isotopes such as deuterium, carbon-13 and nitrogen-15 at specific residues. This, along with particular use of isotope-edited NMR techniques, has permitted us to characterize the local conformation and dynamics of the peptide while bound to its receptor protein. Without such isotopic labelling, it would normally be extremely difficult to directly derive information about the peptide in these complexes using NMR. Three examples of protein-peptide complexes investigated this way will be discussed. Each of these corresponds to an antibody-peptide complex in which the peptide was isotopically labelled at several different residues to enable investigation of the bound peptide. Information obtained from these isotope-edited NMR studies has included conformation of the bound peptide as well as delineation of those peptide residues important for antibody binding. The latter was based upon changes in the local dynamics and environment of peptide residues due to formation of the complex. From these techniques, it was possible to obtain physical information from the bound peptide of these complexes at an atomic level. For two of the complexes studied, the physical information obtained this way has important implications regarding the potential development of synthetic vaccines against AIDS.

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### **MECHANISMS OF COMPLEXATION OF ALKALI METAL CATION-CALIXARENE COMPLEXES VIA $^{23}\text{Na}$ AND $^{133}\text{Cs}$ NMR SPECTROSCOPY**

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The complexation of  $\text{Cs}^+$  and  $\text{Na}^+$  by a conformationally flexible calix[4]arene in 1:1 binary mixture of deuterated chloroform and deuterated acetonitrile was studied by  $^{23}\text{Na}$ - and  $^{133}\text{Cs}$  NMR spectroscopy. The ability of the sodium and cesium cations to be selectively recognized respectively by the cone or the partial cone conformers of the calix[4]arene is demonstrated.

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### **Preparation of no-carrier-added MIBG via Solid Phase Organic Chemistry**

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Solid phase organic synthesis using a polymer supported arystannane provides unique advantages in the synthesis of radiopharmaceuticals. The radio-iodide can be used as the limiting reagent and the desired radiopharmaceutical can be readily separated from unreacted polymeric starting material and from polymeric side products by filtration. This approach has

been applied to the preparation of m-iodobenzylguanidium (MIBO) which is of clinical interest both diagnostically and therapeutically.

An insoluble polymeric solid support has been prepared in which 3-benzylguanidine is attached as an aryltrialkylstannane as shown below. The synthesis of this polymer will be described as well as characterization of precursors by MAS solid-state NMR spectroscopy (C-13 and Sn-119) and by HPLC identification of products of halogenation and protodesstannylation. It has been shown that this polymer can release up to 1.1 mmol of MIBG/g of polymer. Reaction of this polymer with radioiodide (NaI-123 and NaI-131) and an oxidant results in efficient formation of no-carrier-added radioiodinated MIBG in high chemical and isotopic purity.

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### **Production Techniques of Stable Metal Isotopes: Current Status and Future Trends**

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The February 1, 1998 shutdown of the ORNL calutrons signaled a loss of the world's production capacity for stable metal isotopes. This occurred at a critical time, as the major market for these products, namely the radiopharmaceutical industry, has undergone a shift from diagnostic agents to ones that are therapeutic in nature. Thus the demand for new agents and hence their precursors is increasing substantially. Through advances in technology and with the support of several isotope facilities in Russia and Siberia little or no impact will be felt on the world market with the ORNL closing. A collaborative effort, co-ordinated by Trace Sciences International, has enabled a unique production partnership to form. A "strategic alliance" between, Elektrokhimprebor, Urenco, The Kurchatov institute, and Tomsk has enabled the world capacity to not only expand but to do so in a co-ordinated manner. EKP and Kurchatov act as primary and secondary manufacturers for Calutron produced isotopes whereas Urenco and Tomsk perform this function for centrifuge based elements. This alliance has given great support the radiopharmaceutical industry as it moves from diagnostic to therapeutic agents. Advances in centrifuge technology have also decreased the burden on traditional calutron production techniques with the ability to manufacture isotopes of Sn, S, Si, Ir, W, Te. This has allowed the calutrons to become more focused on the production of Sr, Sm, and Pd. Thus ORNL's shutdown has had an overall positive impact in co-ordinating the world production capacity.

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### **Application of Optically Polarized $^{129}\text{Xe}$ to Magnetic Resonance Imaging and Spectroscopy**

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Recent progress in the Optical Polarization of noble gases has opened totally new possibilities in Nuclear Magnetic Resonance and Magnetic Resonance Imaging studies concerning objects or materials with void spaces. Optical pumping can increase the intensity of the NMR signal by up to five orders of magnitude, which makes it possible to do experiments previously only

dreamed about. Perhaps the most spectacular application of Optically Polarized noble gases (HPNG) is as contrast agents in MRI of lungs<sup>1,2</sup>. The area of biological applications involving HPNG is growing rapidly, and clinical tests of this new diagnostic technique have already started. The applications of HPNG in material sciences, however, is still in its infancy. While the first MRI with hyperpolarized (HP) noble gases was reported several years ago, only a very limited amount of work has been done so far on applications of this technique to materials. This approach, nevertheless, is expected to be very promising for analyzing void spaces, pore size distributions, heterogeneity and diffusion properties in a variety of porous materials, including zeolites, aerogels, porous glasses, mesoporous silicates and open cell foams.

The application of this technique has some experimental difficulties associated with it. One of them is the nonrenewable character of polarization in HP xenon, which i) restricts resolution and the choice of MRI experiments and ii) requires some modification of conventional MRI methods when applied in such studies. While <sup>129</sup>Xe MRI images of macroscopic voids in materials are not as spectacular as in living organism, they can reveal important details concerning the geometry and connectivity of void spaces.

The use of HP xenon can provide a great advantage when time resolution is required. In one example we will demonstrate that diffusion of HP Xe into Vycor porous glass can be monitored directly. Another example of temporal resolution is the use of <sup>129</sup>Xe NMR of OP xenon to monitor the formation of xenon clathrate hydrates on the surfaces of D<sub>2</sub>O ice. The exceptionally high sensitivity of the technique allows detailed kinetic studies of hydrate formation with a time resolution of better than 0.1s. It has been found that different types of hydrates can form, depending on the type of the surface and other experimental conditions. Accurate measurements of the relative cage occupancies reveal a higher occupancy of the small cages at the initial moments after adsorption compared to the later equilibrium situation. The formation of surface hydrates may require a significant induction period, which can be as long as several minutes. The implications of this work for the development of a molecular mechanism of gas hydrates formation will be discussed.

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### **Production of <sup>142g</sup>Praseodymium in a Small Nuclear Reactor by Szilard-Chalmers Reaction**

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Many compounds of lanthanide metals have been studied with regard to their biochemical and pharmaceutical behavior. A number of rare earth elements have physiological properties which may be of interest in the diagnosis or treatment of certain cancers, and several B-emitting

radioisotopes of the lanthanide series, such as  $^{153}\text{Sm}$ ,  $^{166}\text{Ho}$  and  $^{177}\text{Lu}$ , have been evaluated for a variety of nuclear medical applications.(1)

The neutron-rich praseodymium isotope  $^{142g}\text{Pr}$  also offers suitable nuclear characteristics for internal radiotherapy.  $^{142g}\text{Pr}$  (T<sub>1/2</sub>=19.13 h;  $^{142m}\text{Pr}$ : T<sub>1/2</sub>=14.6 min, 99.4% IT to  $^{142g}\text{Pr}$ ) has B-energies up to 2.16 MeV with approximately 96.3% of the B-particles having an average energy of 0.83 MeV. These particles penetrate approximately 3 mm of soft tissue. During decay,  $^{142g}\text{Pr}$  emits one  $\gamma$ -photon (~1.56 MeV [3.7%]) which does not interfere with internal medical applications due to its relatively low abundance.(2)

$^{142g}\text{Pr}$  can easily be obtained from natural  $^{141}\text{Pr}$  (100%) via neutron irradiation by (n, $\gamma$ ) reaction. The cumulative activation cross section of 11.5 barns for thermal neutrons permits the production of substantial quantities of  $^{142m+g}\text{Pr}$  in a small nuclear reactor.

We investigated the production and enrichment of  $^{142g}\text{Pr}$  using the Szilard-Chalmers reaction in various praseodymium complexes with ligands containing oxygen and nitrogen donor atoms. The complexes were synthesized according to literature methods. Samples of each compound were encapsulated and irradiated in the TRIGA Heidelberg II reactor. After irradiation, the complexes were suspended in water, methanol or DMSO. The aqueous solutions were filtered and the dissolved  $^{142g}\text{Pr}^{3+}$  separated by HPLC or ion exchange chromatography. Radioactivity was measured in a calibrated gamma detector. Yields and enrichment factors will be presented.

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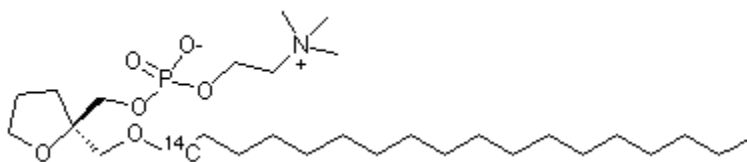
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### **SYNTHESIS OF [ $^{14}\text{C}$ ] MLS-337**

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MLS-337 a new Multiple Sclerosis candidate, labelled with  $^{14}\text{C}$  was required for pharmacokinetic ADME studies. The title compound was synthesized, utilizing 1- [ $^{14}\text{C}$ ] octadecyl-bromide and R-tetrahydro-2-[(phenylmethoxy)methyl-2-furanmethanol. The alkyl bromide was obtained in the following manner: treatment of 1-bromoheptadecane with  $\text{K}^{14}\text{CN}$  gave labelled alkyl nitrile, which was hydrolyzed to the acid by the action of acetic acid/sulfuric acid/water. The carboxyl function was next converted in two steps to the required [ $^{14}\text{C}$ ]bromo intermediate. The benzyl-protected labelled ether was synthesized by coupling of the protected chiral tetrahydrofuran dimethanol with alkylating agent. Deprotection was straightforward and drug substance was obtained in a three-step, one pot operation. The details of the synthesis will be presented.




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## Palladium-103 - Radionuclide Source for Brachiotherapy of the Prostate

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Cancer of prostate takes the second place among oncology diseases for men. At present the most effective method of treatment of this disease is brachiotherapy (endocurietherapy). Such therapy implies that the closed source containing an appropriate radionuclide, is placed either on surface (brachio) or is immersed inside the tumor body (endo).

A tiny radioactive source (0.8 x4.5 mm) is implanted directly inside the tumor. The standard course of treatment involves implantation of at least 20 sources per patient. The main requirement of the sources for brachiotherapy is high specific activity of radionuclide.

The following items are discussed in the presented work:

- technology of making of enriched  $^{102}\text{Pd}$  (62%);
- theoretical calculation of the optimal irradiation condition in the nuclear reactor;
- manufacturing technology for closed radioactive sources of  $^{103}\text{Pd}$  in a shape of a needle, disc or sphere.

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## MRI OF HYPERPOLARIZED XENON

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Laser-polarization of  $^{129}\text{Xe}$  creates a very non-equilibrium state of the system of spins, enhancing the polarization by four to five orders of magnitude. This huge signal available can be used as a powerful probe for MRI. The recent availability of large amounts of hyperpolarized  $^{129}\text{Xe}$  gas may allow novel MR imaging techniques such as imaging of gas spaces like the lungs or blood flow measurements.

However, because hyperpolarized  $^{129}\text{Xe}$  is in a non-equilibrium state, the longitudinal magnetization depolarizes exponentially with time until it reaches a Boltzmann thermal

equilibrium, and the portion of the longitudinal magnetization tipped into the transverse plane, when an RF pulse is applied, can not be recovered. These two losses have an important impact on MRI with hyperpolarized Xe. First, T1 of xenon in blood and other organs of interest has to be as long as the time to carry the xenon from either the lungs or the injection site to the target tissue to avoid a significant loss of hyperpolarization. Second, the imaging pulse sequence needs to make efficient use of the available non-recoverable magnetization. Knowledge of T1 and T2 is the first step in the development of imaging sequences suitable for hyperpolarized xenon imaging.

To determine the signal improvement possible with a cylindrical cell of diameter 1.7 mm containing 0.7 atm of natural abundance xenon (26.4% of  $^{129}\text{Xe}$ ), two spectra of a xenon gas sample were obtained with and without hyperpolarization. This is shown in figure 1. The relative improvement in SNR provided by 25 minutes of hyperpolarization was  $1.8 \times 10^3$ . Our preliminary results also demonstrate the feasibility of imaging hyperpolarized xenon in the gas phase, as can be seen in figure 2, showing a transverse image of the cell. This image is the result of two averages acquired with a constant flip angle of about 80. Xenon in a saline solution was also investigated, its spectrum indicates that imaging of both gas and dissolved phases of xenon should also be feasible.

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### **Application of NMR Spectroscopy to the Direct Measurement of Oxygen-17 Abundance in Heavy Water**

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Processes used for heavy water production also change the relative abundances of the oxygen isotopes. For nuclear power applications, where the heavy water may be exposed to a neutron flux, the abundance of  $^{17}\text{O}$  affects the amount of  $^{14}\text{C}$  generated through the reaction  $^{17}\text{O}(n,\alpha)^{14}\text{C}$ . Reference methods based on mass spectrometry for the determination of  $^{17}\text{O}$  isotopic abundance are subject to isotopic fractionation and are time-consuming to perform. Isotopic fractionation is not a factor in the non-destructive analysis of  $^{17}\text{O}$  by oxygen-17 NMR spectroscopy. Development of this application is described, including the determination of key parameters, such as spin-lattice relaxation time, line width, sensitivity, and precision and accuracy in the measurement.

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### **CANADIAN RECOMMENDED ENERGY INTAKES UNDERESTIMATE REQUIREMENT IN MIDDLE-AGED AND ELDERLY WOMEN AS DETERMINED BY DOUBLY-LABELLED WATER**

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The Recommended Nutrient Intakes for Canadians (RNIC) are important in calculating funding for institutional care and other programs which provide social assistance. The objective was to determine whether the RNIC provide a true index of energy requirement.

Energy needs, assessed using multimedia diet recording of intake and by doubly-labelled water (DLW) were compared to tabulated RNIC levels. Dietary intake was estimated by combining the use of a micro-cassette tape recorder and 35 mm camera by 56 subjects ( $67 \pm 1.6$  y (49-93y),  $63 \pm 1.5$  kg., BMI  $24.8 \pm 0.6$ ). Using household measures, subjects voice-recorded and photographed all food and beverages consumed and leftover for 4 days. A modified two-point DLW method was used over 13 days to calculate energy expenditure and total body water. The RNIC suggested a requirement of  $7.2 \text{ MJ} \pm 0.2$  for these subjects which showed no significant difference between the reported energy intakes ( $7.7 \text{ MJ} \pm 0.3$ ). All stratified age groups 49-59, 60-69, 70-79, 80-93 years reported an average protein and caloric consumption that was adequate according to the RNIC with a mean of 16% protein, 54% carbohydrate, and 28% fat. The multimedia record mean energy intakes underestimated energy expenditure by 22% as determined by DLW.  $9.9 \text{ MJ/d} \pm 0.4$  ( $p < 0.01$ ). The multimedia diet records and the RNIC both underestimated requirements when compared to DLW. This study concludes that use of tabulated RNIC's underestimated true requirements as determined by DLW. This may explain why the energy recommendations are low, because previous self-reported records which were used to calculate the standards do not reflect true intake. (Supported by N.H.R.D.P. 6605-1644-201).

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### High Current Encapsulated Target System for Radioisotope Production

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"Solid target" Systems for use with vertically oriented targets are currently used at TRIUMF for radioisotope production. In order to irradiate liquids, powders, and non-electroplatable materials using the newly developed encapsulated target, a new target system for use with horizontally oriented targets is being designed. This target station has a modular assembly consisting of a landing terminal, an irradiation chamber, a manipulator, and an actuator. Targets are pneumatically transferred between the station and the hot cells. The target is positioned in the irradiation orientation by a remotely controlled actuator, which also creates a concentric coolant circuit against the back surface of the target. Additional cooling is provided by a forced flow of helium gas over the top surface of the target. This target station can also be used for irradiation of regular solid targets.

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### THE EFFECT OF ION-PAIRING ON THE STRUCTURE OF THE $S_N2$ TRANSITION STATE

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The secondary alpha deuterium kinetic isotope effects found for the  $S_N2$  reactions between thiophenoxide ion and n-butyl chloride show that the transition state is very different when the nucleophile is a free ion and when it is a solvent separated ion-pair in DMSO, in DMF and in methanol. However, when the nucleophile is phenoxide ion and the nucleophilic atom is oxygen rather than sulfur, ion-pairing does not affect the secondary alpha deuterium kinetic isotope effect in the  $S_N2$  reaction. Chlorine (leaving group) kinetic isotope effects are used in conjunction with secondary alpha deuterium kinetic isotope effects to demonstrate that ion-pairing alters the  $S_N2$  transition state when the nucleophilic atom is sulfur but not when the nucleophilic atom is oxygen.

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