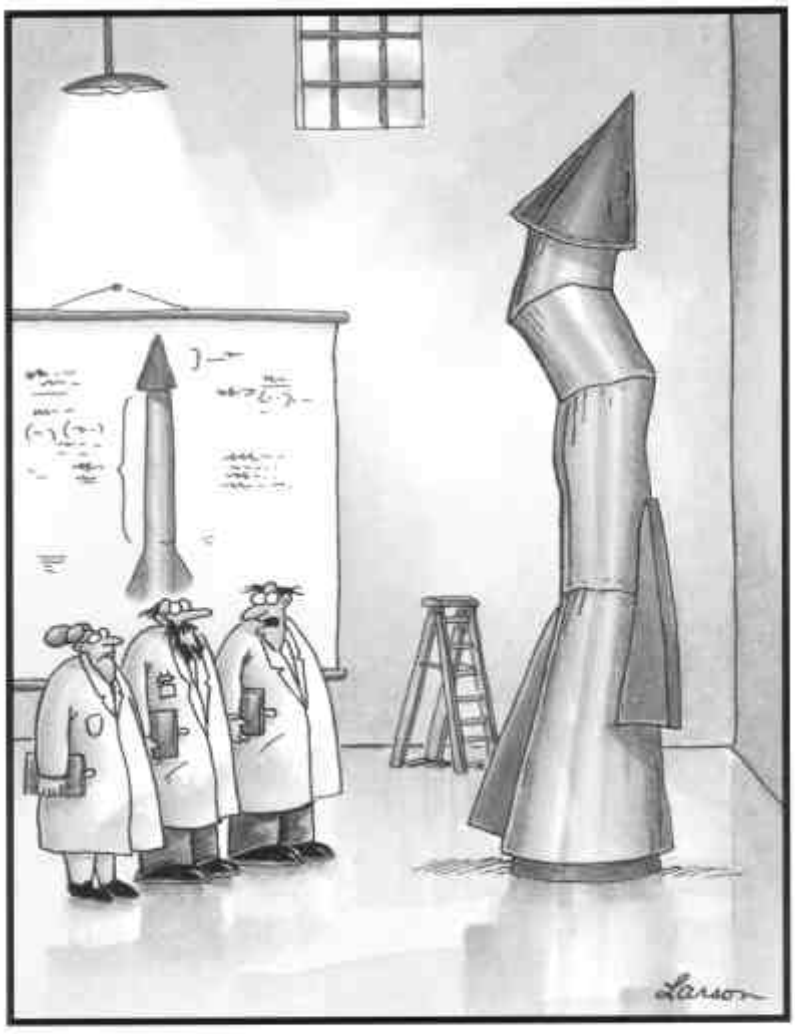
First Session

Accelerators and Targets
Users' Experience
New Facilities
Report from the Labs

Co-Chairs: John C. Clark
Mikael Jensen



"It's time we face reality, my friends. ...
We're not exactly rocket scientists."

The GE ^{18}F-Fluoride High Yield Target, Results and Experiences

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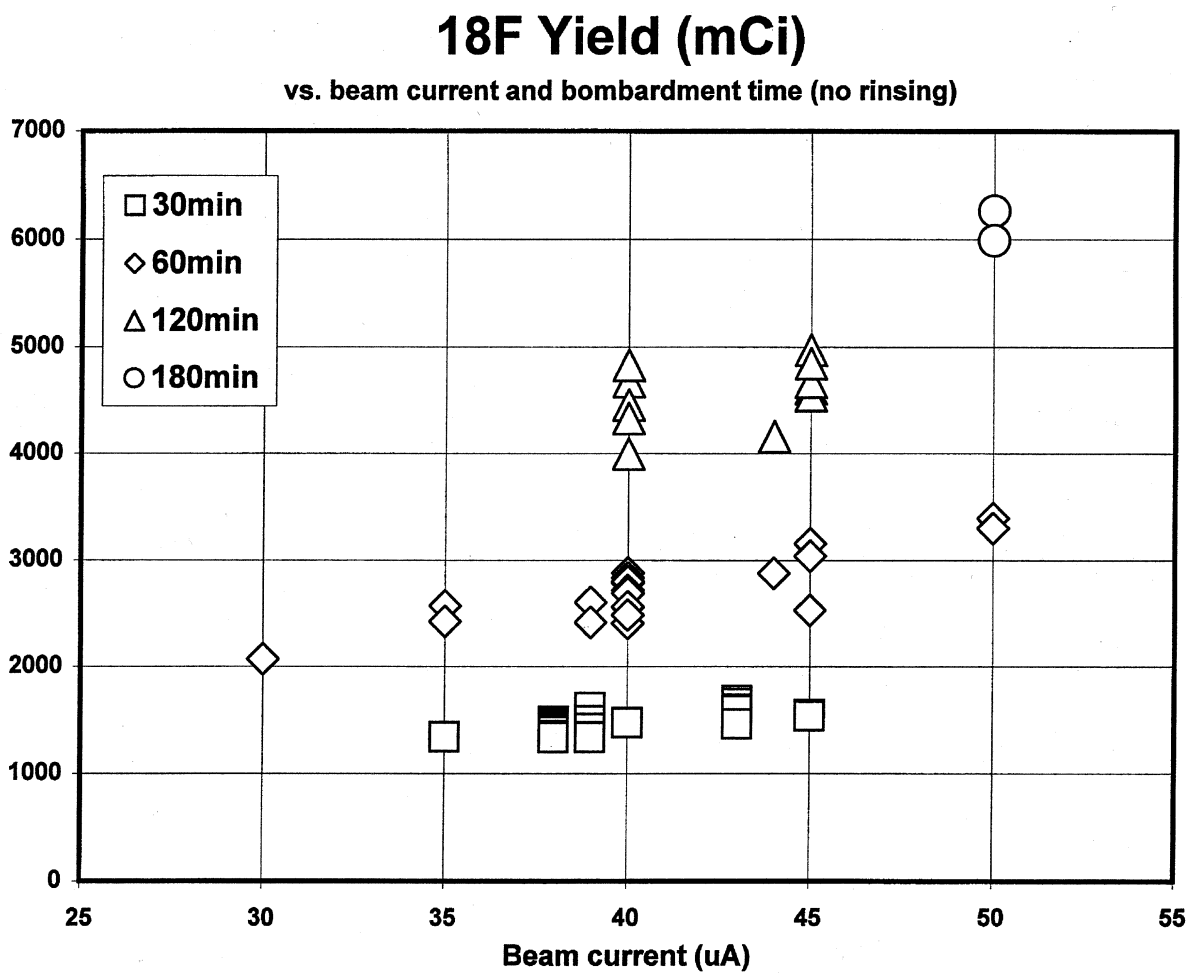
A ^{18}F-fluoride target for high yields has been developed to meet the production rates required by regional distribution centers of FDG and also to match the dual beam current capacity of the 16,5 MeV *PETtrace* cyclotron. The *PETtrace* standard ^{18}F-fluoride target design (limited beam current, low pressure) had an hourly production rate in the order of 1200-1500 mCi. Sensitivity to enriched water quality, target handling and preparation also called for further development to reach a reproducible and satisfactory production rate.

Encouraging experiments with a slightly modified standard target operated at high pressure (30 Bar) made us believe that we could raise the performance of the standard target without too much design efforts and a development program was outlined. The evolution process led to a target design with very high and reliable yield characteristics.

The target is operated at high pressure (30-40 bar) and has a volume of 850 µL. Good production characteristics with reliable output at high beam currents and long bombardment times have been typical. Single target batches in the range of 6 Ci have been achieved (3h @ 50 µA) and FDG batches in the range of 2.5 Ci EOS have been produced.



Discussion:

Q: T. Tewson: Do you make any attempt to balance the pressure on the target with the pressure of the helium cooling? In other words, do you try to keep the pressure a minimum accross the window?

A: No. The burst pressure is 70 bars for the target window.

Tewson: I worried more about the bulging in the window than the bursting, because it affects the volume a lot in a small volume target.

A: It's about 0.7 mm for 30 bars, it goes up to about 1.2 mm just before the burst.

C: R. Ehrenkaufer: Just a quick comment on the dual target irradiation. Since we're going into production at Bowman Gray for shipping FDG, on the RDS-112 we will be doing dual irradiation on fluorine targets. We get about 1.1 Curie now in a 2 hour run, so we should get over 2 Curie of fluoride from dual targets, so you are wondering about the actual use of the dual irradiation?

Q: J. Steinbach: About the target cleaning. What are you actually doing ?

A: Opening the target and then we can see a very thin layer, a grey layer at the silver surface. It's very easy to remove and it comes back to full performance just by brushing off that and have some ultrasonic cleaning assistance.

C.: I think it's enough to clean only with ethanol and to dry.

A: I think everyone agrees upon the value of Scotch Bright.

C. R. Ferrieri: One comment about cleaning a target with an organic solvent. We had an accident about 5-6 years ago when we had ppb levels of ethanol in our O-18 water. The water target put out huge quantities of ^{18}F, but we couldn't make any FDG with it. I would strongly urge you not use any organic solvent within the target, no matter how well you wash it you're going to wind up with still some trace of organic in the surfaces of the target.

Q: Could you give a number for the saturation activity at the end of the irradiation ?

A: It depends a bit on the beam intensity but we are in the range 180 to 200 mCi/μA.

Improvement of Fluoride-18 Production in IBA Targets

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The growing number of PET centers and the successful developments of coincidence 511 KeV collimated SPECT cameras have increased the popularity of 2-[^{18}F]fluoro-2-deoxy-D-glucose as a tracer for nuclear imaging. Consequently, there is a growing demand for this radiopharmaceutical compound. The nucleophilic [1] introduction of fluoride-18 on 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethane sulfonate-ß-D-mannopyranose is certainly the most convenient synthesis route to obtain large amounts of 2-[^{18}F]fluoro-1,3,4,6-tetra-*O*-acetyl-D-glucose. In such a case, fluoride-18 is produced by the ^{18}O(p,n)^{18}F nuclear reaction on oxygen-18 enriched water.

IBA has developed a small volume target (300 µL cavity volume) and a large volume target (1700 µL cavity volume) which are commercially available. With the purpose of increasing the production yield, a new target design has been studied. Two major changes were made. The first change concerns the modeling of the internal cavity. The cylindrical cavity of the small volume target has been replaced by an hemispherical back wall. The aim of this work was to optimize beam penetration in the target cavity, and thus to increase the production yield (see table 1).

Two major changes have been done on the large volume target. An hemispherical back wall replaces the bottom of the enriched water cavity, and the heat exchange surface of the target body has been increased. The two modifications have led to an increase of the beam intensity and an optimization of the beam penetration (see table 2). A value of 5.2 Ci has been measured after 2.5 hours bombardment at 18 MeV with a beam intensity of 33 µA.
These features have led to an important increase of the target yield and have reduced the pressure inside the target during the irradiations. With these new targets, multi curie of fluoride-18 can be produced.

Table 1:

	Enrichment (%)	Volume (µL)(1)	Material	Energy (MeV)	Irradiation Time (minute)	Beam Intensity (µA)	Activity EOB (Ci)
Cylindrical Target	97	350	Ag	10	60	20-25	0.6
Hemi-Spherical Target	97	410	Ag	10	60	30-35	1.1

Table 2:

	Enrichment (%)	Volume (µL)(1)	Material	Energy (MeV)	Irradiation Time (minute)	Beam Intensity (µA)	Activity EOB (Ci)
Cylindrical Target	97	1700	Ag	18	60	20-25	1.6
Hemi-Spherical Target	97	1810	Ag	18	60	30-35	3.0

Reference:

[1] K. Hamacher, H.H. Coenen, G. Stöcklin, Efficient stereospecific synthesis of no-carrier-added 2-[^{18}F]fluoro-1,3,4,6-tetra-*O*-acetyl-D-glucose using aminopolyether-supported nucleophilic substitution, J. Nucl. Med. **27**: 235-238 (1986)

Discussion:

Q: R. Hichwa: How long does your target last before you have to clean it?

A: You can use one month without any cleaning if you want. If the target works well you have to plot a graph the yield of the target. When you see something wrong it's time to start the cleaning. But if everything is ok, you continue to make irradiation without doing anything.

Q: R. Hichwa: And how do you clean it?

A: With ethanol and drying with helium. One other advantage of this target compared to the old one, it's very easy to clean, because you don't have any corners.

Q. F. Helus: What is the construction material?

A. This is a silver insert and around you have a copper screw.

Q: K. Dowsett: What sort of window material are you using?

A: Havar window, 25 micron.

Dowsett: What sort of burst pressure are you getting?

A: 20 bar (during irradiation).

Q: K. Erdman: How much headspace? What is the volume if you totally fill the cavity ?

A: Total fill is 1.8 mL for the large volume target.

C: M. Haka: We have those targets and at 20 µA, those foils always blow. We have very little flexibility, we run them at 15 µA, and we make 800 mCi. We have the cyclone-30 and degrade the energy to 18 MeV.

Q: A. Roberts: What is the window diameter?

A: Window diameter is 10 mm.

C: J.-L. Morelle: This is a comment about the dead space. We fill the target using a syringe in such a way that there is always a bubble left above the target, so there is some void space for water expansion. The second thing is somebody asked what is the rupture pressure by the operating pressure. The operating pressure is 20 bars, but the rupture pressure is probably between 40 and 50 bars.

Evaluation of the General Electric PETtrace™ Radio Tracer Production System

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During February 1997, the three authors were invited to Uppsala, Sweden to evaluate the PETtrace™ cyclotron and ancillary equipment. None of the three authors have financial or other ties with GE Medical Systems (GEMS). The authors after a short (1-1/2 hour) training session, carried out production runs on the system. GEMS staff operated the chemistry units (methyl iodide and FDG microlab) and carried out the analytical quality control on all the radiopharmaceuticals produced. The goal of the visit was to provide an independent assessment as to the capabilities of the PETtrace™ system. In a two-day period oxygen-15 gases, oxygen-15 water, nitrogen-13 ammonia, carbon-11 carbon monoxide, carbon-11 carbon dioxide, carbon-11 cyanide and carbon-11 methyl iodide were all produced. Fluorine-18 was produced with yields as high as 5 Ci with 1.3 Ci of FDG being produced. Dual target bombardment was utilized to produce carbon-11 and fluorine-18 precursor simultaneously. The characteristics of the PETtrace™ system will be described.

Discussion:

Q: Can you comment on that magnet ramping ? You have to ramp it down ? What's that all about ?

A: S. Lindbäck: We have been running this way, but we're going to change that. It is an easy software change.

A : We worked out a way to do it, but it's sort of the way the program is set up, between the runs you have to ramp it down.

Q: F. Helus: I would like to ask about the reasonable amount of the activity because it's nice to make eventually 4 or 5 Ci per day. But if somebody would like eventually to produce five days per week and 50 weeks a year is it reasonable to make this high activity? For commercial production maybe, but for two or three PETs?

A: M. Welch: It's sort of interesting, Sally Schwarz has a poster on our FDG experience. We are feeding four PET scanners. We have many days where we do six FDG patients and make at least two other ^{18}F radiopharmaceuticals. So if we have 5 Ci and can put half of it into the FDG box and keep half to make the other things, I think we can use 5 Ci a day with no problem

Q: Jensen: You mentioned the low yield in the box for the FDG. Is that 5 Ci of good stuff, good water, or has it junk in there from irradiating on so hard? How far does the yield drop ?

A: I can hypothesize. I don't think I know and I don't think the GE people know either!

Q: Did you do anything else with that water to show that that 5 Ci is good stuff ?

A: No.

C: M. Orbe: We have discovered that probably the resin is affected. As you all know by now we are using the resin-based method, we believe that we get some radiation damage when we put in high activities, that's why our yields are leveling off. We have tested this amount of F^- together with the Nuclear Interface system and we have produced 2.5 Ci of FDG. So it's still good F^- . To the best of our knowledge it's usable stuff.

C: R. Ferrieri: Mike, you mentioned making 5 Ci F-18 distributed over the various uses. Has anyone considered how to distribute the target load as it comes out whether you run it to a resin station, recover your water or take the entire water charge. This is something we're facing now: How do we cut off our F-18 without overly exposing our personnel. We want to minimize hand manipulation.

C: G. Gaehle: We use our robotic system to split it up in the different pigs for individual users. We do extraction or we can just take the straight water and split it up.

Bill Alvord, CTI Inc.: RDS-111 Targetry

I'd like to echo John's comment that the best testimony, the best information probably comes from our users, so I'd rather give Jim O'Neill some more time and be brief here and summarize as quick as possible.

This is a photo of both the targets and the target changer of the RDS-111, which is our current offering. The target changer holds eight targets, they are series cooled in the water and they are singularly He-cooled, in other words only the target that's in the extraction position gets helium for the target window. They are modular, they have a little target cooling flange and the window as you can see up there. So this is the window, this is the target cooling flange, this is the target and these are the external cooling threads for the water cooling. It holds all five of our current isotope production targets which are C-11 in the form of CO_2 , O-15 in the form of O_2, a fluoride target, N-13 in the form of ammonia and F-18 in the form of F_2.

What we tried to do is have a single cooling path for the water and the helium so that we don't have chances of leaks, make it easy to maintain, and easy to get at quickly since you are in a radiation environment. There is a hole right here in the target, the umbilical contains one captive screw so you can install the target with one screw and remove it with one screw.

This is a cross section of the target changer, there is a rotating barrel, this is one target pocket, this is another one and there are eight around this axis. The collimator is a ring collimator, a graphite ring and a vacuum window. The assembly can be removed without disassembling the target changer, you move one target and pull the vacuum window assembly out. This is typical of the target, this is just the target you saw here, I'm going a little bit into more detail of the F minus target but I really let Jim detail that. It's a silver body target, all the other target bodies are aluminum and have a Havar window. All the target windows are 25 micron Havar except the ammonia, which is a titanium window.

Discussion:

Q: Do I understand you just have one vacuum window which is fixed and each target is presented to that?

A: Yes.

Q: Is dual beam irradiation possible?

A: Yes, it's a dual port machine, so you have any combination of the 8 and the 1 target changer and the 8 and the other target changer.

Q: What is your collimator diameter?

A: 8 mm collimator, and we have about a 72% transmission through that.

Q: Can you give a value for the $^{11}CO_2$ specific activity ?

A: Our specification is 25 Ci per micromol. We really have like 50 Ci per micromol. That's straight out of the target. The tests we've done have been immediatly at the target and I think that's important to distinguish between that and your final post processing figure.

Q: How did you measure?

A: We cold-trapped the gas coming right out of the target and then did GC on it.

Q: J.-O. Bergström: What's the maximum beam current you can run on the targets ?

A: 40 µA on all the targets.

J. O'Neil, Lawrence Berkeley Lab: User Experience - The No.1 Machine in Berkeley CTR RDS-111

(C: John Clark: "The most traveled cyclotron in the world")

I honestly didn't bring to many slides to do an overview on what our full range of production is right now, but we've got a few here and we've got a poster talking specifically about the high pressure fluoride target that CTI developed and we've been using in our machine since last fall. Here is a picture of the machine and our current staff along with Glen Seaborg who is in training right now with us! This was done during our dedication ceremony, we had the pleasure of having Glen there.

This is my picture of the silver body fluoride target. The target we are currently running has a baseball diamond shaped pocket in it. So this is an about five mm deep pocket and it has got a rounded top on it for a reflux chamber although we overfill this target to the tune of about an extra 250 µL of enriched water to backfill. So the ventline is actually filled along with the valves above the target.

As Bill mentioned, the foil, the window in these targets is in our case 7 mm targets but CTI are moving up towards an eight mm diameter collimator now. The target is machined out of a solid silver ingot, and as Bill mentioned, the target flange to bring in the cooling helium is machined from aluminum. Running 25 micron Havar, we are running that target at 48 bar without any window failures so far in several hundred runs.

So currently at Berkeley what this machine is doing right now is mainly fluoride and fluorine production. We are making FDG about three days a week, we are making fluoro-metatyrosine through electrophilic fluorine the other two days a week for animal studies, (dopaminergic studies). The remainder of the time is spent making fluoride for radiopharmaceutical development. We have an occasional span where the doctors will show up and want ammonia, but that's probably bimonthly at the most. So currently we do not a lot of ammonia production.

One thing we did do was pretty interesting last year and I want to comment on it. It was the first solid target that we ran on that machine. We actually had a fellow from nuclear engineering who was interested in making some Beryllium-7, and we actually redesigned a target to hold a Lithium-7 pellet and then we had a copper holder that we dropped into the aluminum target. We were able to bombard it under an argon atmosphere to make Beryllium-7. And we got somewhat towards the theoretical yield of Beryllium-7.

And as Bill was pointing out, with the turret changer it is handy because with one screw and really a long stick with threads on it you can stand back and pull these targets and get them into pigs.

I think the only other comment I have from the user's standpoint is that as long as you are not playing with it or doing new target development it continues to be a low maintenance machine. It's relatively simple to operate, much like the 112 as far as the user interface is concerned.

Discussion:

Q: A. Roberts: Are all of your targets on this target changer, or is your F_2 target one of those like the RDS-112 installation?

A: Yes, our F_2 target is currently a 112 gas target. When we first started the machine we used the fixed one. We have a fixture to run 112 targets on the second beam line. We run a low-pressure fluoride target and we still run our F_2 out there. We haven't finished designing up a 111 target for that. We're in the process of doing that and we're also in the process of setting up our oxygen and carbon, so we don't have any experience there.

Q: So the only things you're doing with the 111 targets is the fluoride and the ammonia?

A: Yes.

Q: B. Mock: What is the actual beam current you are running at the high-pressure fluoride target?

A: We've run up to 40 µA. This was a very early one and not on this target. We ran 40 µA a few times and it seemed to pretty much take the target out at that point. The target yields would drop on the next run. We routinely run 30 µA on it without any problems. I've got some data on the poster that show that the saturation starts to fall off drastically about 35 µA on this target. Bill's been working on that problem as far as redesigning the targets.

Q: B. Mock: How often do you have to clean the target ?

A: Depending on the current we're running. Staying in the 20 - 30 µA range, the last cleaning we had was about 40 runs ago.

C: J. Nickles: Just a simple comment about the ^{7}Li to ^{7}Be and the ^{103}Pd and a few other things. If we look around, we are the OPEC of a number of missions here, albeit it radiotherapy or astrophysics ... .

A: This ^{7}Be was being made for this neutrino problem.

A Collaboration Between PET Cyclotrons CYCLONE 18/9 User Community

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History
IBA cyclotrons are widespread in PET application meanwhile. During the initial installation and operation phase of the first PET cyclotrons of CYCLONE 18/9 type the idea came to light that it would be necessary and very helpful to come in close contact to all other CYCLONE 18/9 users. Consequently, in 1994 Stephan Preusche initiated and elaborated the CYCLONE 18/9 USER COMMUNITY.

Aims
- to come in contact with all other CYCLONE 18/9 users
- to have competent partners for discussion and
- to exchange experiences of operation and maintenance of CYCLONE 18/9 including chemistry and chemistry modules

All CYCLONE 18/9 facilities (existing and under planning) around the world agreed, and our institute organized the first workshop of the new community in Rossendorf in October 1996 [1]. All together 25 colleagues of the following facilities took part in the first workshop:
- Herz- und Diabeteszentrum NRW, Bad Oeynhausen/Germany
- Hôpital Cantonal Universitaire de Genève/Switzerland
- IBA, Louvain-la-Neuve/Belgium
- Hadassah-Hebrew University Medical Centers, Jerusalem/Israel
- Montreal Neurological Institute/Canada
- Nuclear Interface, Münster/Germany
- Clinica Universitaria - Universidad de Navarra, Pamplona/Spain
- Forschungszentrum Rossendorf/Germany
- Biomedical Research Foundation of NW Louisiana, Shreveport/USA
- Universität Ulm/Germany

The workshop started with the introduction of each facility, followed by a visiting program to get an impression of the Rossendorf PET Center. Most of the time was dedicated to discussions of the following topics:
- operation of CYCLONE 18/9: experiences of operation, hints and tricks, safety aspects, interlock system
- environmental care: measures to prevent or minimize emission of radionuclides
- chemistry modules: experiences of operation, hints and tricks
- maintenance and service (CYCLONE 18/9 and chemistry modules): experiences, most important failures and how to prevent them, most important spare parts, problems of troubleshooting, helpful tools
- special hints for facilities that are still in planning phase or under installation.

At the end of the workshop all participants recommended to continue the meeting and to involve the few CYCLONE 10/5 cyclotrons. The workshops should take place every 2-3 years and will go the round. The next workshop will be organized by the CYCLONE 10/5 facility of the University of Leuven/Belgium in late spring or early autumn 1998.

Reference:
[1] CYCLONE 18/9 USER COMMUNITY, first workshop, Rossendorf, Germany, October 10-11 1996, FZR-151 (1996)

Discussion:

Q: M. Welch: Can you tell us a bit about how the machine works? Because rumor has it the Montreal machine still hasn't matched spec's.

A: Our machine works very well, we didn't have any problems. Maybe you know we got the license in last September and for the last months we worked with our cyclotron. The Montreal cyclotron was the first that was installed from IBA and they had a lot of problems. I was there in November 1994 for 2 weeks, and I saw they had a problem with the ion source. There was something wrong, no good efficiency, some problems too with the efficiency of the extraction so that they don't have an efficiency at some exit ports better than 50%. We have the same type. IBA made big changes from cyclotron to cyclotron. There is another cabelling for RF coming from the top and we have it from the top, the new version has it from the bottom, so it's not necessary to have a moving system for the ion sources. The Montreal 18/9 is not the same 18/9 type that we have. It was the first cyclotron and it's also a question of experience such a firm needs to make such improvements.

C: K. Erdman: I didn't want to say anything on the target design itself, I just want to comment that there are other ways to put a target port on a machine. Because the H minus machines do have extraction, you can simultanously change the energy as well as the current out the individual ports and this is of course very useful when we talk about the efficiencies and what the best energy is for doing various types of isotope production. When you do that, the angle that the beam comes out of the cyclotron changes with energy so you have to design your target differently. And in that connection the EBCO cyclotron has a target head which is mounted on a bellows. So typically this is running sideways, there is the bellows here, this is like a shower head that you can swing in various different directions, the targets are mounted at the end of this and it swings above the target line. So you can have a multiplicity of targets on here that can be used for either a water target for fluorine ion production or a gas target for doing the F_2 production, or you can have ammonia, various different targets and you can have them on the individual lines out of the cyclotron. So there are other ways of putting target ports on that allow you to put multiple targets on in small volumes and also allow you to change the energy of the cyclotron at which you extract the beam. I just wanted to make that comment.

C: M. Jensen: (Comment on Scanditronix targets) Some of us are still living with the MC17 cyclotrons and the related targetry and some of the bigger cyclotrons are also using the MC17 PET targetry and we have experienced that Scanditronix, when Scanditronix are alive, can actually host these usergroup meetings and can support us with still valuable information on these targets. So even though there are not so many new machines coming out, it can be valuable, and I hope that Scanditronix will host those usergroup meetings also in the future and keep the chemistry alive.

C: M. Welch: I would like to make a comment on that. GE and we organized a US group meeting of people who use their FDG box to assist in putting together a NDA, and they where very helpful. It does help to organize usergroups.

Mikael Jensen: Selection of the Optimal Cyclotron

It is not an easy thing to talk on what's the ideal accelerator and what is the optimum energy. Everyone has an opinion on that. For less than five radionuclides - and we are all talking about the same end products – do we need all these machines? This is more than one machine per nuclide. Is this related to capitalistic proliferation or are there too many cyclotron engineers out there eager to help us solve problems that are already solved? Or are we still fighting to get an optimal design? Apart from all the energies and that we have the question coming up, is the cyclic accelerator, is the cyclotron really the optimum design and should we go to superconducting magnet technology?

Most people here are still using the word cyclotron meaning a classical resistive type magnet. Another question I would like to put as a provocation for discussion: Some of us have to produce ^{15}O-water 8 or 12 hours a day, even on night shifts for sleep studies, dream studies, whatever. We need 2.5 µA or less of 6 MeV deuterons. Is this really the same machine which has to deliver 30, 50 µA, perhaps dual beam for two targets at 16 MeV protons? Can anybody tell me whether it's really optimal to design a machine capable of doing those?

I have noted that more and more users and companies are beginning to differentiate between a local PET supply and a regional PET supply. Does that mean that if you are only supplying yourself locally, you can have a low cost cyclotron but if your are thinking about going for regional supply you need a bigger and better machine? Or will the companies claim that their machines can do regional supply? What you are trying to optimize should be that number: perhaps it is mega-dollars and mega-bucks and not kilo-bucks. It depends on whether you are looking at invested or the running costs. You have to add that together. And you have one number missing here. The invested capital, how long is that going to last? How long are these cyclotrons going to stay there and operate?

I saw no number whatsoever from any of the manufacturers relating to that important figure. This is what we really need to calculate the optimal machine, because this is mCi per kilo-dollar. This is one question I would like to put to each the manufacturers. Will they maintain their cyclotrons running and for how many years? A final question for both the users and the companies to react on: During this session I heard about GE new target going on a CS15 machine, is that right?

A: Yes.

C: Jensen: This is interesting, it means you don't have to stick with one company, you can pick what you like. If this is true, if this is going to work..

C: M. Welch: We are taking a chance by this, because we are paying the money and they will guarantee a year.
Could we get into a situation where we could pick the optimum target independent on our machines ? I think we are not in that position now. I believe there is some capitalism involved in this also. I think the manufacturers will tend to keep a design which is forcing us to use their targets. From the point of view of all the researchers and end users we would like to swap targets to pick the optimal target design from one company. I would like to ask the companies if they would comment on the lifetime of their cyclotrons?

C: S. Lindbäck: They last too long!

Jensen: Apart from this statement, Stig, do you really know that on the PET trace? Have you thought about it, when you did the design? Have you done anything about it?

C: S. Lindbäck: It's the same kind of basic design features, you know, engineering.... Quality you see on the '17 and they have been around in '81, '82. People are thinking about swapping these now, but that's because of the electronics are becoming obsolete, control system electronics in particular.

C: Jensen: So a life of at least 15-20 years?

C: S. Lindbäck: Yes.

C: D. Schlyer: There's a cyclotron that has been running for over 40 years, in Brookhaven!

C: R. Dahl: Sloan Kettering cyclotron is among the oldest. It was installed in 1967, it's still running, and yet we should remember the Crocker machine is still in use and that is actually older than me!

C: M. Welch: We pulled the "Allis Chalmers" cyclotron out after 25 years and there were people who cried and thought we did a terrible thing by pulling it out because it was still running. Our CS15 although it was installed in the '70s was in fact built for UCLA in 1969 and sat in a warehouse for 8 years.

C: K. Erdmann: The big problem with positive ion cyclotrons used to be that they became highly radioactive. The amount of radioactivity that you produce at these current levels is not sufficient to destroy any of the permanent bits of equipment you have inside. The only thing you could have problems with is the magnet coils, but those can be replaced. The rest is basically forever, except O-rings you may have to change after seven years, but those are just components.

C: M. Welch: Karl raised the question of decommissioning cyclotrons. You know we decommissioned the "Allis Chalmers" and MGH decommissioned their "Allis Chalmers", and we both took similar routes. They rented space in a corner of a junk yard and just left it there for 8 years and then gave it to the junk yard because it wasn't radioactive. We stored ours for 8 years and then sold it to scrap. We did the calculations independently and we both came up with the fact that we could store the yoke for 8 years and then sell it as non-radioactive.

C: J. Clark: The old Hammersmith cyclotron is still at Hammersmith, being used as shielding.

C: K. Dowsett: It seems we are looking at two factors here. One is the lifetime of the electronics with the manufacturer who is to support or to provide valves for power systems that are 20 years old, they may not exist any more and you have to have them custom made. And the other one is, modern cyclotrons are using less and less power so it becomes cost effective at some point to replace the cyclotron and reduce the running costs by buying one that uses maybe a tenth of the power of the old machines. Both are the factors that limit the lifetime.

C: J. Nickles: I believe we have the oldest CTI RDS cyclotron, 12 years old, and after our recent maintenance period we wanted to make sure we can still meet spec's. We did it and had over 50 μA on the target.

C: I think when I looked at all the machines around the world in that particular field the only one I found that was decommissioned was the prototype CGR machine from Pisa and that was replaced by a PETtrace. And Montreal, that was the early Japan Steel machine.

C: Jensen: Is it true that you need a bigger and better machine for doing regional supply?

C: S. Lindbäck: How much do you want - 2 Curies, or 3 Curies? 5 Curies? A Curie isn't enough to supply a whole country!

C: Jensen: It depends on the size of operation. Some of the commercial radiopharmaceutical companies are approaching some of the cyclotron centers and some of the PET centers and asking whether they can sub-supply. And then the big companies can do the shipping and logistic and the marketing and then we are talking about as much as you can do. 10 Ci of FDG coming out of combined sites in Europe every day. I guess some in the audience have experience of how much is needed for regional supply.

C: E. D. Carroll: I am in Riyyad, we are a couple of thousand miles from the next cyclotron and supply a vast area. We have a CS30 and we are supplying all of the thallium and gallium and iodine as well as doing a little PET. But we now start to get other hospitals that want FDG and they don't have PETs, they are all SPECTs with 511 collimators. And that would mean that we soon need multiple Curies fairly going out of the hospital and it depends on how far away things are. We have customers they want to have their own cyclotron. We are talking about throwing away several half-lives before it even gets to them. How much you want to make depends on how far away your customers are.

Q: J. Clark: Is there anyone here from industry who may have putting together business plans for regional distribution of FDG who is willing to put in on this? Amersham, Mallinckrodt? Anyone else? Time is microcurie or millicurie, isn't it, unfortunately. Fluoride was distributed in the States before PET was invented.

C: H. Schweickert: I'm not from industry but we are doing a lot of production for a region of about 300 km around Karlsruhe. And our actual need is in a maximum about 2 Ci per day. But we assume that in the next two years we will need about 3 Ci per day. And at the moment we are using a CP42 H minus cyclotron which is by far too large for this type of production, there is no doubt. And my impression is that a good 20 MeV machine can do for sure the same job but the most serious problems for routine production is nowadays a pharmaceutical point of view. If I look into the effort we have to do to get a license and fill the licence by components, by hardware and by people, this is by far a much more serious problem than the cyclotron and the FDG module. And this is for my point of view not taken into account by many people especially not by the sellers of such components because this has to be solved in a region where you are working by the authorities that you are collaborating with in this field.

C: J. Clark: Thank you, I think there were two issues touched on by Mike Welch in terms of getting validation for microlabs and I think the CTI CPCU also got FDA approval. So some of the manufacturers are addressing these issues. But there are whole other areas - I agree - that need addressing. But this forum, I think, could spend another week talking about this subject. It may get raised in other sessions, I'm not sure.

Introduction to Session Ib:
New Facilities and Reports from the Labs

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In this second part of the session we shall have many presentations, reports from the labs, new facilities. There are quite a few facilities that came out of the woodwork last night, consequently my nicely typed up overhead has become a bit scrappy, but never mind, it will work.

As we heard this morning Ruth Shefer is going to give us a brief view of where the TCA is going to these days, straight after Greg Gaehle. The people from Groningen have bitten the bullet to start up their machine completely automatically and we are going to here a bit about that and about making FDG with nobody present.

Nigel Steel from Hammersmith is giving us his perception of trials and tribulations of keeping 5 automated water infusors alive and kicking. We have a new facility, at least an old facility which is going to introduce itself, from Bukarest, Liviu Popa-Simil. They have an old U-120 machine.

Another new facility in Damaskus to be introduced by Abdul Hamed Al Rayyes looks as if it is going to be a Cyclone-30 facility. He has plans, no concrete been poured yet. Maybe he needs to talk to people who had problems pouring concrete etc.

Keith Dowsett is going to give us a snapshot of 10 years of experience with the Cyclone-3 and quality control issues with that machine. Stephan Preusche was put into the previous section. Rich Hichwa will talk about Vanadium-48 transmission sources. Anatoly Razbash has apologized, he doesn't wish to give a verbal but ask you to go and talk to him at his poster.

Jozef Comor is from Belgrade. It's a new cyclotron, big 70 MeV machine and they're planning on making isotopes with it and he is going to share his initial experience there. We have a couple of papers on automation of Fluoro-Dopa. I hope we'll get some compare and contrast on questions with that. Jörg Steinbach is going to stand in for his colleagues and talk about automated fluorinated estradiol. I gather there is quite a bit of interest in that paper, so I expect quite a lively discussion.

Then Andy Roberts, another new facility from Wisconsin, is going to fill us in ‚why not cyclotrons, why use a tandem'. David Schlyer from Brookhaven will talk about something that is called 'LEAF', which I gather is 'Low Energy Accelerator Facility'.

Tom Ruth or one of his colleagues on the TRIUMF site propose to make a virtual isotope center, intriguing thought, together with Dennis Phillips from Los Alamos.

And finally, right at the end of this morning session, Bill Lozowski from the International Target Society is going to introduce himself and what his society is involved in and Tom Ruth who went to the last meeting in Strassbourg will add a few comments at the end of that.

New Approaches to the Control of Accelerators and Production Systems

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Washington University Medical School recently installed a PET scanner in its Neurological Intensive Care Unit to assess viability of trauma patients. Due to the unpredictability of this type of patient, on call production of O-15 radiopharmaceuticals is required. To accommodate this need we have developed a system for the remote operation of the Tandem Cascade Accelerator (TCA) for O-15 radiopharmaceutical production.

Our initial fiber optic network enables control of the TCA from either the Mallinckrodt Imaging Center PET suite or the TCA control room and cost $2000. Due to the distance (2500ft) between the Neurological Intensive Care Unit and the TCA control room, increasing the size of this network would have required expensive fiber optic cabling. A secondary option was to increase the networking capabilities of the TCA control system software. Pyramid Consultants, the programmers of the TCA control system offered to do this at an estimated cost of $35,000. The costly nature of these choices led to investigate an inexpensive alternative.

Our solution was to utilize an inexpensive TCA control network using phone modem connections, operating at a data transfer rate of 28.8 kilobytes per second. We implemented this network allowing file transfer and control of any 486 or higher IBM compatible PC control system using a software product called pcAnywhere (Symantec; $129). Configuration of the network using pcAnywhere can be accomplished using direct serial cables, phone modem connection and/or Internet connection.

The new modem network was established on six computers for approximately $600US dollars. This new network enables us to control and/or monitor the TCA and the accompanying radiopharmaceutical production systems from any of the six satellites. The addition of a satellite simply requires pcAnywhere, a phone line and a 486 IBM compatible computer with a modem. The 28. 8 kilobytes per second operating speed of the network has not hindered the control of the TCA because the actual operational tasks still takes place on the original control system.

PcAnywhere allows the remote system's display and keyboard to function as the host computer's. The transfer of data files is accomplished with a file transfer manager built into the software package. PcAnywhere offers two levels of security (global and individual) and a variety of ways to interconnect and control satellite sites. The personal computer can operate as either a host or a remote system without complicated configuration changes. To prevent outside interference with the system, the host computer can be set to respond to a limited number of identified remote systems, and authorized users can be give login names and passwords for added security. The security system also allows generation of activity reports for any individual using the network.

To date we have experienced no problems controlling any software package remotely. This includes a host of office and automation programs. Future plans include an Intranet connecting all our PET radiopharmaceutical production units. This will make available all production worksheets and quality control reports of the various production units to all sites

needed at the University. Monitoring from remote sites will allow personnel involved in the automated production of PET radiopharmaceutical to move about the facility while maintaining contact with the production process.

Discussion:

Q: State licensing approval – is that a problem ?

A: We haven't really addressed that, but our radiation safety department seems happy with what we've done.

C: M. Nortier: Just one comment. Our bombardment station at the NAC is run with in-house developed software. It's easier to use PCAnywhere than to try and develop the software in house.

Q: This will of course make irradiation and production of FDG remotely controlled. How long time do you need from production end until you can release your FDG for final use?

A: With this we are just using our O-15 radiopharmaceuticals.

Ruth Shefer, Newton Scientific, Inc.: A Linac for NCT

I was asked to just comment briefly on where the development of these linear machines has gone. This is a new generation machine that Newton Scientific installed at the Massachusetts Institute of Technology about a year and a half ago. It is a tandem accelerator with much higher current capabilities than a van de Graaf or belt type charge machines. This is a 4 MeV machine, it's higher energy than the one at Washington University. We have run it up to about 800 µA of protons. It runs with protons or deuterons. It was not built for PET, but as a neutron source for boron neutron capture therapy. That's what it's being used for, it's being used to produce neutrons both on lithium and beryllium targets. We have also used it to make N-13 for the production of positron beams, again, not for PET.

Q: Nickles: Have you considered harvesting the lithium target for the beryllium-7 people ?

A: No we haven't, but that's an interesting idea. We will consider it.

Fluorine-18 Production via the $^{18}O(p,n)^{18}F$ Reaction Using the PULSAR™ PL-7 RF Proton Linac: Results of Initial Target Tests [1]

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Introduction

AccSys Technology first began developing an rf ion linac based system for production of positron isotopes in 1985 [2]. PULSAR™ consists of a PL-7 rf proton linac for acceleration of H^+ to 7.0 MeV with integrated targets and shielding for production of positron isotopes and positron labeled radiotracers. The status of development and remaining challenges of PULSAR™ were most recently discussed in 1995 [3].

Experimental Methods

The accelerator used for these initial target tests was the prototype PL-7. This rf proton accelerator has been described in detail elsewhere [4]. Briefly, however. the PL-7 is a proton only accelerator with an energy of 7.0 MeV which is achieved by closely coupling a 3.0 MeV RFQ section with a short 4.0 MeV DTL section to boost the final proton energy to 7.0 MeV. The prototype accelerator was operated with a beam duty factor of 0.12% at a pulse repetition rate of 10 Hz.

The proton injector used for the PL-7 during these tests was a duoplasmatron based ion injector for deuterons running in the proton mode at up to 5 μA peak current and 10 Hz to match the linac repetition rate.

A stainless steel beam fine of 76.4 cm (30 in.) length and 2.23 cm (7/8 in.) ID was attached to the high energy end of the PL-7 and the target was attached to the beam line.

The prototype target used by the PL-7 for producing fluorine-18 via the $^{18}O(p\ n)^{18}F$ reaction was developed in cooperation with Dr. David Schlyer's chemistry group at Brookhaven National Laboratory under a Department of Energy Cooperative Research and Development Agreement (CRADA) [5]. The target body was machined from titanium with an internal volume of 810 μL. The front foil was 0.001 in. thick (1 mil) Havar supported with an aluminum "grid" which was 50 % transparent to the beam. Energy loss in this foil was approximately 1.0 MeV for 7.0 MeV protons incident. giving a 6.0 MeV proton beam on the ^{18}O-water. All other target components were machined from aluminum. Immediately prior to an irradiation, the target was manually filled through PE tubing with 2 % oxygen-18 water and run at 75 psig air overpressure.

The initial target irradiation was for 15 min at three μA of proton beam current with the target filled with ^{16}O-water to assure target integrity. Three individual one hour irradiations at 3-4 μA were performed during the next two days. During these longer irradiations the target overpressure slowly increased to 140 psig at the end of one hour. All irradiated water was recovered within two min of end of bombardment (EOB). After the final one hour irradiation, the emptied target was rinsed with water to determine the completeness of recovery of the fluorine-18 produced.

Results

Inspection of the target at the end of these tests showed no evidence of any effect on the target assembly front foil or foil support "grid". Over 95 % of beam passed through the collimator onto the target and comparable amounts of activity were produced in each of the one hour irradiations. Based on theoretical calculations using a gamma-ray dose constant, Γ,

of 4.4 R/mCi at one cm distance for fluorine-18 [6], the amounts of activity produced in the first and third one hour irradiations were: 350 and 420 µCi, respectively. This is shown in Table 1. The activity measured in a calibrated dose calibrator at 83 min post EOB for the fluorine-18 produced during the second one hour irradiation was 223 µCi. This is equivalent to 393 µCi at EOB.

In the one test run in which the target was rinsed with water after emptying, over 98 % of the fluorine-18 was recovered directly with the initial emptying of the target.

Table 1: Fluorine-18 produced during the three one hour irradiations on 2 % ^{18}O-water at 3-4 µA

Run Date	Survey Meter (mR/hr @ 8 in.)	Calculated (µCi)	Dose Calibrator (µCi)
11/19/96	4.7	440	370*
11/20/96	5.0	470	393
11/21/96	5.5	530	440*

* Corrected values derived from the measured ratio (393/470 = 0.794) between the survey meter based calculation and the dose calibrator result for sample 2 (11/20/96).

Gamma-ray spectra of samples recovered from the target after the initial test (^{16}O-water for 15 min) and the first two one hour irradiation (2 % ^{18}O-water) are shown in Figures 3 and 4.

Conclusions

The results of these initial studies using the 7.0 MeV beam from the Model PL-7 rf proton linac to produce fluorine-18 via the ^{18}O(p,n)^{18}F nuclear reaction confirm the viability of this approach to production of PET isotopes.

Extrapolation of these results at limited beam currents suggest that the PULSAR™ specification of 1.500 mCi of fluorine-18 will be achieved with a one hour irradiation at 100 µA using a target configuration similar to that of the prototype unit. Demonstration of such performance with the first production PULSAR™ 7E will be in the near future.

Studies are now underway to use a 5.0 MeV deuteron beam from a DL-5 rf deuteron linac to verify the robustness of our initial fluorine-18 target design at higher beam currents than were available during the initial tests reported here. The lower energy deuterons pose a greater challenge for two reasons: (1) deuterons have a higher dE/dx than protons and (2) dE/dx will be greater at the lower energy (5.0 MeV vs 7.0 MeV).

A redesigned "next generation" target for fluorine-18 production via the ^{18}O(p,n)^{18}F reaction. which incorporates improvements such as those suggested above will be included when the first production PULSAR™ unit, which is built around the PL-7 linac for this application. is delivered in late 1997.

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APPENDIX: Data on Radionuclides Commonly Used in Nuclear Medicine Imaging (Normal Subjects).

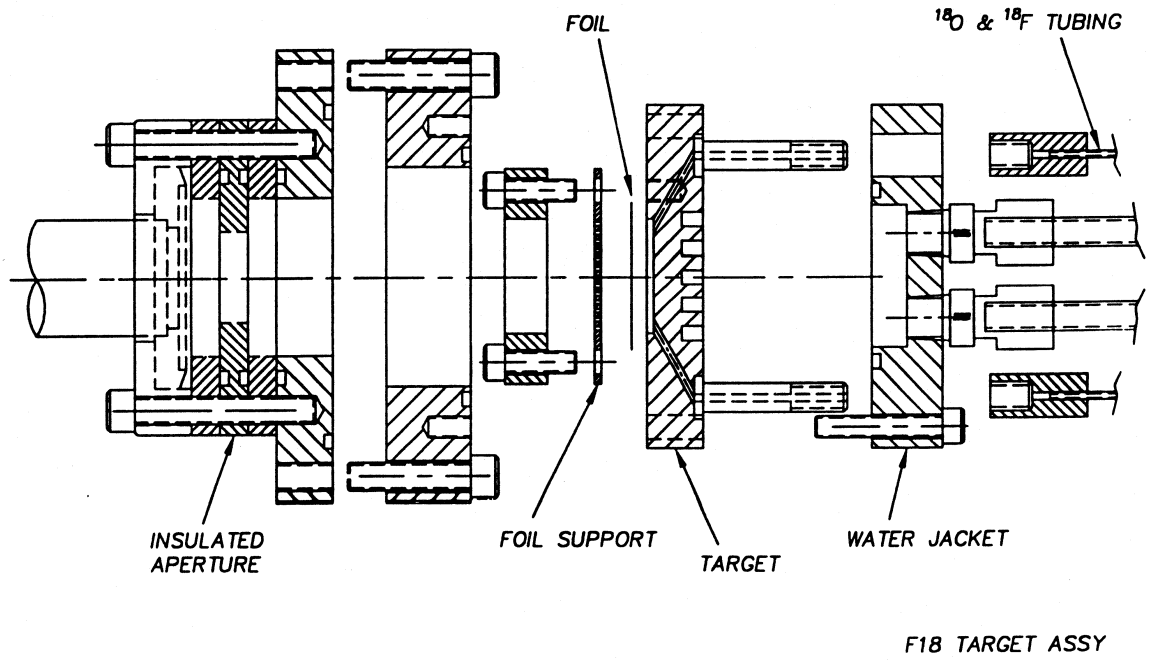

Fig. 1: Assembly drawing of prototype target used for initial tests of fluorine-18 production via $^{18}O(p,n)^{18}F$ reaction with the PL-7 rf proton linac

Fully Automated and Unattended [^{18}F]Fluoride and [^{18}F]FDG Production Using PLC Controlled Systems

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2-[^{18}F]FDG is the most widely applied PET-tracer for clinical use. Besides application in PET-centers, FDG is now also distributed to hospitals with SPECT-facilities. Ideally FDG should be available at 08.00 a.m., this requires the overnight production of FDG. We report a fully automated production method without presence of personnel. The goal of our automation is an unattended production of FDG with a high reliability and reproducibility during nighttime without personnel costs. These items are also important if FDG has to be available very early in the morning for further distribution to hospitals within a range of one half-life (2 hours).

The process is divided in two parts:

1. Irradiations are performed by the Scanditronix MC-17 cyclotron with a proton beam with a fixed energy of 17 MeV. The target consists of an aluminum and silver body with a volume of 1.0 mL operated under a helium overpressure of 14 psi. The entrance foil is from Havar (25 µm) while the backplate is from silver (0.25 mm). Performance: 800 mCi $^{18}F^-$ EOB at 18 µA for 60 min [1]. The cyclotron and targetsystem is controlled by a Siemens PLC (type 135U) which runs under the STEP-5 program.

2. After [^{18}F]fluoride is produced via the $^{18}O(p,n)^{18}F$ nuclear reaction in ^{18}O-enriched water the [^{18}F]FDG is produced by recovering the [^{18}F]fluoride via the resin method and the cryptate drying process [2]. After alkaline hydrolysis [3] the mixture is purified by commercially available cartridges [4].The processing unit is set on a gliding system to facilitate preparation and maintenance. The synthesis is controlled by a B&R programmable logic controller (type: Midi-control) with 16 analogue inputs, 8 analogue outputs, 24 digital inputs and 48 digital outputs.

The unattended sequence with the different steps is summarized below:

	Time (min)	**action**
1	0	cyclotron stand-by / setting fluoride production
2	15	conditioning deflector
3	45	set proton mode
4	60	target filling
5	61	autotuning
6	62	irradiation
7	EOB	emptying target
8	2 EOB	FDG-synthesis
9	45 EOB	Formulation

1. The cyclotron is switched on at a predetermined time. Also the appropriate target, beam current (12 µA) and beam particle are selected. Stabilization of the radiofrequency (RF) is realized.
2. The deflector is conditioned by switching the ion-source on air (flow: 3 mL/min), thus avoiding conditioning during working hours.
3. Ion-source is switched back to H_2 for complete removal of air.

4. In order to increase the reliability, the target is overfilled (1.5 mL) by a precision ceramic pump; the number of fillings is registrated.
5. The proton beam is switched on by an autotuning sequence, the presets are shown below.

autotuning sequence	***presets***
internal beam	9 µA
ion-source output	> 1 µA/mA
extraction to external beam	> 50 %
transmission to F.C.	> 45 %
transmission to F^- target	> 30 %
<u>utility interlocks:</u>	
high and low limits parameters	setpoints
overcurrent trip probe	100 µA
overcurrent trip F.C.	75 µA
overcurrent trip target	20 µA
overpressure target	25 psi

This autotuning process has a reliability of > 98 % (n = 60) in case of one attempt, the failure rate is further minimized by the use of 5 attempts with intervals of 1 minute.
6. The irradiation takes place till a preselected integrated beam current or time is reached. The target pressure is monitored by a pressure transducer with is positioned in the helium fine.
7. When integrated beam current or time is reached the [^{18}F]fluoride is transported by helium overpressure over about 10 m to the FDG-module.
8. The irradiated enriched water is registrated and triggers the FDG-module. Radioactivity and liquid detection results in a complete recovery of the [^{18}F]fluoride from the recovery column. In-line temperature measurement in the reaction vessel results in a reliable and reproducible process. Preparation of the reagents are performed on the day before after an automated washing (water and ethanol) and testing program (leak and flow tests).
9. The final product is isotonic, colorless, sterile and pyrogen free and is suitable for clinical use.

In conclusion, a reliable unattended production (> 96 %) method has been developed. Evaluation is in progress whether external signaling is needed to improve the reliability.

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<u>Discussion:</u>

Q: How did you control the PLC? That's an MC17? Or what cyclotron do you have?

A: Yes, MC17 from Scanditronix, it's a Step 5 programming.

Q: And how did you make it automated or unattended?

A: There sits my colleague, he's a specialist.

Q: Is it controlled by the PLC or by the computer?

A: Just by the PLC. Most of the MC17 users know the option of the step5 programming.

C: It's not an easy task to use the PLC as a computer, making it start at the day of demand and time of demand. It's a specialists job.

Q: T. Ruth: Other than your low yield or something, what is your failure rate in terms of is it a quality control issue or just the yield? You said 4 % failure.

A: The 4% failure was of the outer tuning, from the whole sequence. So his could be outer tuning of cyclotron. Also the cyclotron itself could be shut off.

Q: Ruth: What do you use for quality control to release it if this is totally unattended? At what point would someone know that this is not good?

A: When the FDG is ready, of course we do a quality control, we do HPLC, TLC, the common quality control,... Than that takes about half an hour, but at 8 o'clock in the morning, our FDG is ready for use.

C: J.-L. Morelle: You just spoke about quality control, so at that point and all the unattended operations you went up to the synthesis module. I suppose you are not working on a unattended quality control yet?

A: No! It's excluding the quality control.

Q: B. Mock: When you're doing the FDG, setting up the night before, when do you dissolve your triflate precursor? Is that dissolved the night before or do you have it set up to be dissolved at the time of use?

A: We dissolve it already late in the day, so it stands of course more than 10 hours maybe. The vessels are closed. We dissolved the precursor also before. So when we fill the PLC, then we dissolve the precursor.

Q: And your yields?

A: This is maybe why our yields are still not so spectacularly high. But you have unattended FDG and for internal use you have no costs for personel, so for your own hospital you have enough FDG.

Maintenance and Quality Assurance of a Bed-Side [^{15}O]water Infuser

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The hands-off bed-side device used at the MRC Cyclotron Unit to generate [^{15}O]water from cyclotron produced [^{15}O]oxygen and to deliver the solution for PET measurements of cerebral or myocardial blood flow in human subjects has been described in some detail [1]. Three infusers have been in routine use in our Unit for several years, providing studies in up to six patients daily, and delivering over 200 GBq of [^{15}O]water in a typical week. This heavy workload has led to a requirement to develop a network of complex procedures, both for maintaining the equipment and for assuring the quality and efficacy of the delivered [^{15}O]water.

It is essential for the administered [^{15}O]water to be both sterile and apyrogenic. Carefull design of the generator hardware can minimize risks of contamination and pyrogenicity, but it is important to have monitoring procedures in place. The generator is continuously flushed with sterile saline to prevent any build-up of micro-organisms, with an additional high flow rate flush each morning before the first PET study (Scheme 1). In addition, once per week, the generator is flushed with 0.1% sodium hypochlorite solution (Scheme 2). Before use, external filters and lines are replaced and water samples are sent to the in house quality control laboratory for tests of apyrogenicity by LAL (Limulus Amoebocyte Lysate) assay.

Sterility of the [^{15}O]water was initially checked for every subject administration. Now that reliability has been demonstrated, sterility is tested twice weekly on the outlet filter and on a sample of water from the generator. The filter is tested by Hammersmith Hospital pharmacy by backflushing it with tryptic soy broth and incubating the sample. The water sample is tested in accordance with BP requirements by International Laboratory Services (Derby, UK). Additionally, before removal of the hardware, the system is flushed with 50 % tryptic soy broth solution through all fluid paths and samples sent to Hammersmith Hospital pharmacy for incubation. The system is then immediately flushed with saline to remove all traces of the broth solution.

Every two months the [^{15}O]water production hardware is removed for maintenance and a new set installed. Maintenance includes *i)* checking valves for evidence of saline leakage, *ii)* inspecting the membrane exchanger block for radiation damage, *iii)* autoclaving the exchanger block, *iv)* replacing the membrane in a clean environment, *v)* He pressure testing the gas paths, vi) leak testing the fluid paths, and *vii)* sterilizing the completed assembly with 0.1 % sodium hypochlorite solution. Spare hardware sets are drained of saline, plugged and stored dry.

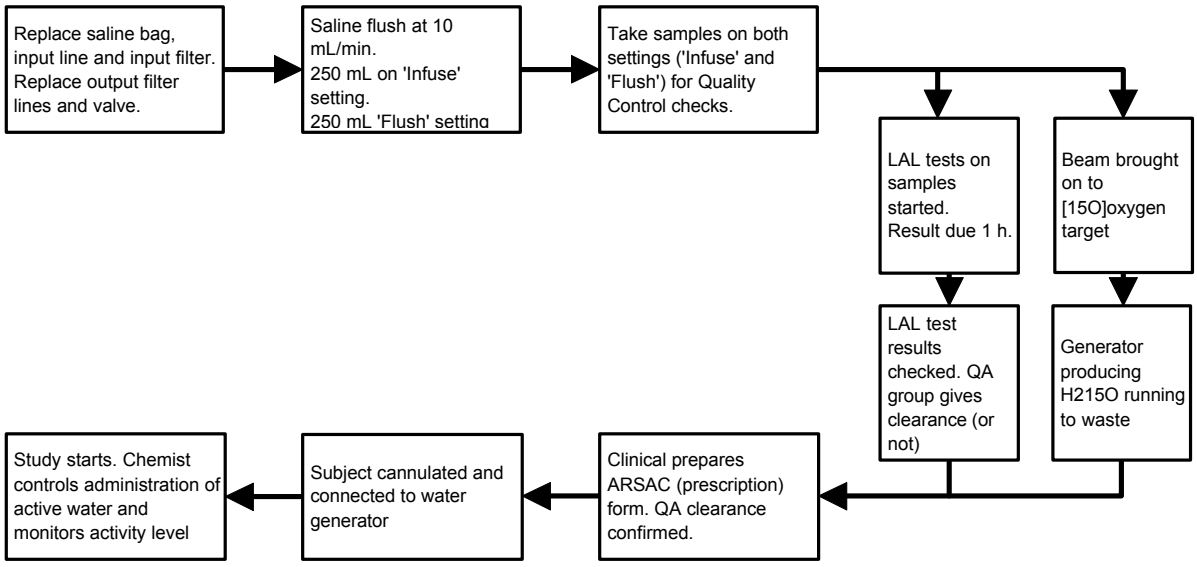
It is also important to quantify the amount of radioactive material delivered. Unlike PET radiopharmaceuticals produced and administered in batches, [^{15}O]water produced continuously and on-line cannot be taken to an ionization chamber for measurement. Instead the built-in radioactivity detector is calibrated against an ionization chamber as part of maintenance. There are also daily spot-checks to guard against equipment failures and detector drift.

The control software for this system is in two parts. The water control panel contains a micro-processor which handles the data acquisition and infusion timings. This stand-alone system is used to overcome problems with timing using the PC clock. It also provides a high level of reliability because the software is stored in EPROM on the controller board and is consequently much less likely to be corrupted than programs on the hard disk of a PC. This communicates with the PC software through an RS-232 interface.

The user interface and logging facilities are provided by a PC running software under Windows. This provides a graphical user interface which offers functionality including:

- Monitoring and controlling the heater and valves
- Flushing of the system when not in use or as p art of a sterilization procedure
- Preparation of samples for LAL testing by the QC laboratory
- Convenient entry and storage of protocols for water administration
- Enforced entry of an ARSAC[2] number before infusion can proceed
- Logging the batch numbers of all the sterile components (lines, filters, check valves and saline) used in the preparation
- Logging the names of the operators and clinicians as well as the isotope request details
- Logging the amounts of radioactivity infused and the start and stop times

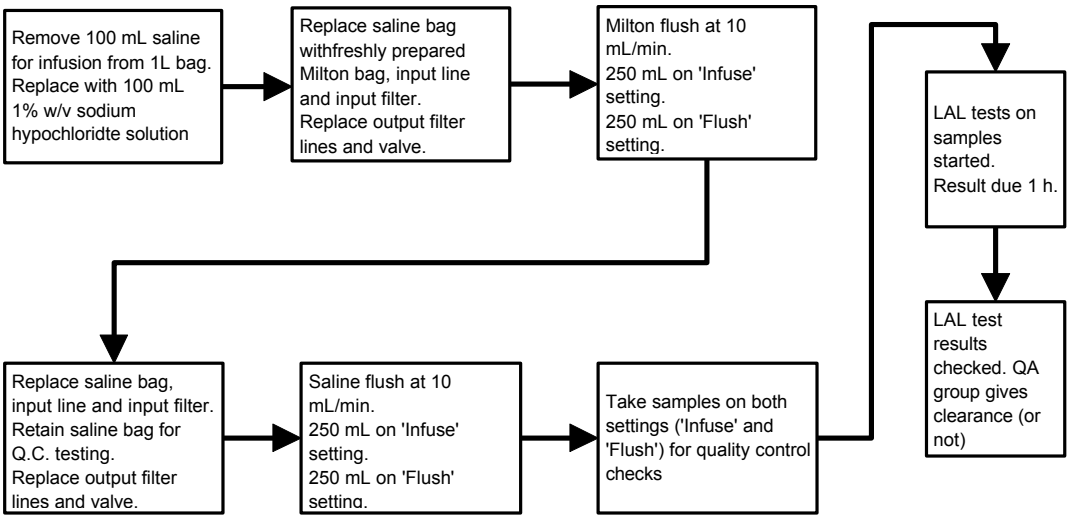
The data recorded by this program is important both for data analysis and as part of the regulatory system.



Scheme 1: Flow Chart of Morning Start-up Procedure Before First Study of Each Day

These protocols and procedures have been developed to ensure that the infuser and its use meet or exceed all the requirements of the local regulatory authorities.

[2] ARSAC is an acronym for 'Administration of Radioactive Substances Advisory Committee' who must give approval for the administration of radioactive substances to human subjects in the UK.



Scheme 2: Flow Chart of Weekly 'Milton Sanitisation' Procedure

Reference:

[1] H.-J. Tochon-Danguy, J.C. Clark, A. Janus, J.I. Sachinidis, Technical performance and operating procedure of a bedside [^{15}O]water infuser. *J. Label. Compd. Radiopharm.,* **37**: 662-664 (1995)

Discussion:

Q: M. Jensen: How many persons are involved? Can this be done by one person?

A: One person can run the generator, yes. We have a separate person from quality assurance to do the LAL tests. So it's actually independent from the operator. And the incubations are done over in the hospital pharmacy rather than on site.

Q: P. Angelberger: How do you evaluate your LAL test? Just by visual inspection?

A: Yes, if it's clotted, then it'll fail.

Q: You don't use a instrumental measuring device?

A: No.

A Versatile ^{15}O-Water Infusor

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R. Schwarzbach
Paul Scherrer Institute, Villigen, Switzerland

A water infusor was built, based on the device described by Clark and Tochon-Danguy (Proceedings of the 4th International Targetry Workshop, 234-5, 1991, Villigen, Switzerland). The layout is shown in Scheme 1.

Collaboration with the suppliers of the infusion pump and the radioactivity monitor allowed for a versatile "stand alone" water infusor:

The computer of the radioactivity monitor (VRM 202, Veenstra Instruments, Marie Curiewei 1, 8500 AC Joure, The Netherlands, Tel. 0031/5134/16964, Fax. 0031/5134/16919) was modified by the manufacturer to allow the following additional functions:

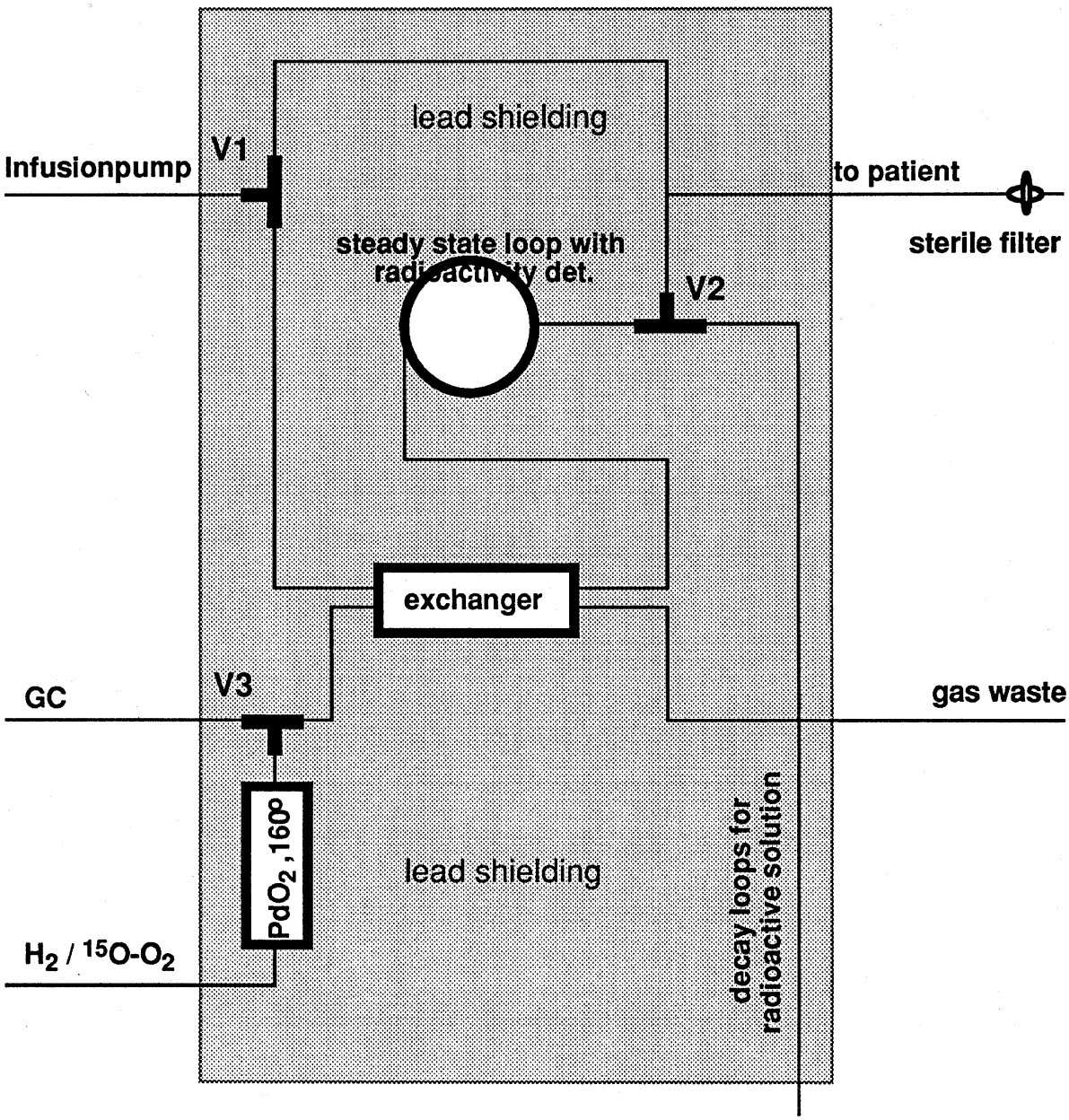
- control of the three-way valves V1 and V2.
- control of the choice of the two preset flow rates of the infusion pump
- continuous display of the steady state radioactivity in the loop, display of the accumulated radioactivity after an injection cycle.

The infusion pump (Arcomed µVP 5000, Arcomed AG, Althardstrasse 146, 8105 Regensdorf, Switzerland, Tel. 0041/1/8404740, Fax 0041/1/8400649) was modified by the manufacturer to allow for two possible flow rates: the side displaying the total volume infused can now be used to set a second flow rate. Thus the pump can be set to deliver a slow steady state flow rate and a fast "injection" rate, which allows for a reproducible input function. Also a switch was installed by our hospital electric shop to silence the audio alarm, to allow for undisturbed brain activation studies.

The three way valves V1 and V2 were switched via relays (also possible to do it by hand), V3 by hand. V3 switches the gas flow (mixture of H_2 and O_2/H_2O in N_2 just after the PdO_2 catalyst) to a gaschromatograph to allow for quality control.

The membrane in the infusor was Visking Dialysis Tubing (Medicell Int. Ltd., 239 Liverpool Road, London N1 1LX, UK, Tel. 0044/171/6072295, Fax 0044/171/7004156)

Function:
By pressing the "enter" button on the Veenstra control unit, the steady state pump speed of the infusion pump is switched to the faster "injection" speed. Three seconds later V2 is switched on for a pre set time, followed by V1. After a second preset period everything returns to the starting position. This sequence pumps the steady state loop activity to the patient during the preset time and rinses the tubing afterwards. Both times can be programmed. During this time the radioactivity detector integrates all the activity going to the patient and displays this as a total number afterwards.



Scheme 1

Liviu Popa-Simil: Report from Bukarest, Romania

We operate the U-120 cyclotron which is delivering proton beams up to 30 MeV and α-particles up to 27 MeV. What is interesting is that this machine is classical cyclotrons with adjustable energy, but it's quite a little bit difficult to handle the energy and the field and the resonance conditions, but it may be done. We can deliver internal beams up to 200....300 μA, external beams up to 40....80 μA. It depends on the time and the state of the art conditions. It works sometimes.

You see, it's quite an obsolete machine, made in 1956, bought from the Russians and it was quite a reliable machine what was interesting. Now it's in a level of our technology and we can maintain it by ourselves and operate it quite independently.

The interest for radioisotope production started in the early seventies by an enthusiastic team which made research for production over seven or ten years. They established some of the basic production reactions, they made a lot of measurements in that time. Their enthusiasm froze in 1977 because of the reorganisation of the institute. After that period, only laboratory tests have been done, but what they achieved at least was the target positioning inside the dees with a device which permits the introduction of the target and also the rotation and cooling of this device. When the target is taken out, it will switch and go to a hot cell for mechanical processing.

Talking about radioisotope production, we produce Cd-109, Fe-55 for XRF application, I-123 (only a small amount, a few hundred millicuries for an experimental hospital application), and laboratory test of Ga-61, Na-22, Mn-54 and also short-lived radioisotopes like C-11 and F-18.

After the solid targets have been irradiated in our laboratory, the target is moved to another laboratory which we call the Center for Radioisotope Production. This laboratory was an investment made in 1977 and it's main job is to use the radioactive elements produced by our nuclear reactor VVR-1, also a Russian type, commissioned in 1956. They are producing some radiopharmaceuticals, technetium generators to deliver to our hospitals, tritium labelled compounds I-131 for thyroid function and also some Ir-192 for medical application and also for gamma ray sources, calibration devices. Basically that's all about our facilities, they are quite a bit obsolete but still operational. Because of the changes in our policy we are now interested doing PET applications and starting isotope production again for medical purposes.

Discussion:

Q: J. Clark: Does anybody know how many U-120s are still operating?

A: F. Helus: One in Prague, one in Rossendorf.

C: J. Clark: So you have some partners for a usergroup.

Popa-Simil: We'll try to make a Virtual Center of a few U-120....!

C: F. Helus: The U-120 in Prague has been rebuilt many times and there is now the question if the money invested in rebuilding might not be better invested in buying a new small cyclotron.

Popa-Simil: This is a good idea, we would be interested in a second hand appliance!

C: K. Erdmann: A quick comment on lifetime of a cyclotron. Here is one that's still running 40 years on!

Popa-Simil: It may run in the future, but it's obsolete, we have to change the equipment for control of the beam and for target application. One point why we were not interested in radioisotope production was because we have to irradiate people, you see here some hand operation. We make lot of spare parts but we get nothing in exchange, so it was a big responsibility, very high quality.

C: J. Steinbach: Lifetime was one point with these machines, we at Rossendorf have also this type of machine. It's still running, not for PET purposes now, but you can keep them a long time ok, but these machines have a huge power consumption. If you had the possibility, think over the cost for that, because I think we have a power consumption of more than 300 kW.

A: No, it's about 200 kW, but when you put together the dollars and the kilowatts you think it's better to consume kilowatts.

Abdul Hamed Al Rayyes: Report from Damascus, Syria

In 1995, the Syrian Atomic Energy Commission, in cooperation with IAEA, started a program for a national radiation medical center. This will be near Damascus. This program will be accepted as a model project with IAEA. We just finished the building design of the facility. This is the main entrance of the facility, some clinical offices, stores, this is the controlled area. Here we will have the target room and the cyclotron, a 30 MeV cyclotron. This is the solid target room, R&D target room, PET target room, for the future, iodine target room.

We divided the building into two sections. This section will be for SPECT isotopes like thallium, gallium, indium. The other part of the building will be for PET isotopes. Here we will have room for the PET modules and PET chemistry, quality control and cleaning room. Here we will also have the iodine lab for the I-123 production system. The other part with another separate entrance to a clinical part of the building will have one PET and one SPECT camera for diagnostic applications, directly in this building. The main level of the building will have in the basement all ventilation systems etc. There will be a small first level with offices and biological laboratories.

Discussion:

Q: T. Ruth: When is it due to be completed?

A: We just finished the design of the building. In July this year we will start the construction., which will take two years.

Q: What are your limitations concerning the emission of radionuclides through the exhaust?

A: For the ventilation system we will have some kind of monitoring of the exit of all the gases. The ventilation system of the building is very complicated. We have separate ventilation systems for the iodine laboratory and the target and hot labs, separated systems for the PET section of the building and the other part of the building which is for SPECT isotopes like thallium, gallium.

Experience in the Long-term Regular Production of High Quality PET Gases with the Cyclone 3D ^{15}O Generator

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The prototype IBA Cyclone 3D cyclotron has been in service at Hammersmith Hospital since 1991 [1]. In that time it has run for almost 6,000 h, providing ^{15}O-labelled gases for several thousand PET studies in human subjects. Cyclotron downtime has been less than 2 % (excluding periods for maintenance). The cyclotron accelerates deuterons to 3.4 MeV. The beam, in the range 10 to 50 μA, is incident on a natural nitrogen gas at 25 p.s.i. and effects the $^{14}N(d,n)^{15}O$ reaction. A thin (7 μ) titanium window causes an energy loss of only about 300 keV. The window is cooled by recirculating the target gas. The low beam energy minimises problems due to unwanted nuclear reactions; however, undesirable chemical reactions take place in the target gas plasma [2]. Unwanted products can be reduced by one of several processes *e.g.* cryo-trapping or adsorption on molecular sieve. Each of these methods has pros and cons.

The oxygen-15 is piped directly, as molecular oxygen, to any one of three PET scanners. These are all located 80 m (by gas route) from the cyclotron. The delay in transit causes a significant loss of radioactivity through physical decay. At the scanner, the [^{15}O]oxygen may be converted into [^{15}O]water in a special infuser device for blood flow studies [1,3]. When [^{15}O]carbon monoxide or [^{15}O]carbon dioxide are required for PET studies, the [^{15}O]oxygen is converted into the appropriate chemical form by a gas-processing plant in the cyclotron vault. The plant has been modified to improve reliability, for example by changing furnace tube material, orientation and size, temperature control and operating temperature.

Gas chromatography is used routinely to assess radioactive gas quality. Examples of the maximum contaminant levels allowed are 3.7 % for oxides of nitrogen in [^{15}O]oxygen and 1 % levels for [^{15}O]carbon monoxide in [^{15}O]carbon dioxide and [^{15}O]carbon dioxide in [^{15}O]carbon monoxide. Routine production runs achieve well below these levels.

In conclusion, the Cyclone 3D, coupled to appropriate radioactive gas processing and quality control procedures, provides a highly reliable source of ^{15}O-labelled radiopharmaceuticals for intense PET applications programs.

References:

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[2] J.-C. Clark and P.D. Buckingham, Short-lived Radioactive Gases for Clinical Use,, Butterworths, London, 1975
[3] J.-C. Clark and H. Tochon-Danguy, "R2D2", A bedside (oxygen-15) water infuser, *PSI Proc.* 92-01, pp. 234-235, ISSN1019-6447 *(Proc. 4th Intl. Workshop on Targetry and Target Chemistry,* Villigen, Switzerland, 1991)

Discussion:

C: J. Clark: Can I just comment for those who haven't heard presentations on Cyclone-3 before. The energy is only 3.5 MeV. The cross section for the (d,n) reaction kicks in at about 150-200 KeV. But to conserve energy there is only one 7.5 micron window between the vacuum and the target which runs at about 2 atmospheres and the window is cooled by the target gas in well-proven St. Louis techniques of circulating the gas very rapidly and squirting it at the window. Jean-Luc is in the audience who was the prime mover in getting this machine going from the target end of things. We at Hammersmith juggled with the RF and the engineers from Louvain-la-Neuve to get the machine to run for many hours at a time which is now completely successful.

Q: M. Welch: May I ask a crystal ball type of question. We are still making a lot of water but our demand has dropped enormously over the last two years. The MRI people are doing much more fMRI. If I talk to him, he doesn't think he is going to be doing any water activation in three years. Do other places that do a lot of water see this trend?

A : K. Dowsett: Not at our site, but we have not a strong link with the MRI people. It's water or CO as flow and volume markers primarily. And that's a big part of quantitating the data for traces as well. The cardiac people are using a lot of water studies and there is a third scanner that will probably push up our demands up even further as it comes more on line.

C: J. Clark: Could I just comment that the Function Imaging Laboratories (FIL) center at Queen Square got both fMRI and the Cyclone-3. And they're planning on phasing out PET for flow studies within the next year. So there might be a Cyclone-3 available on the second hand market. We used water for flow studies to go with ligands quite a lot.

Production of Radionuclides for Medical Purposes by the VINCY Cyclotron

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The construction of the VINCY Cyclotron, the main part of the TESLA Accelerator Installation, is in its end phase, and the extraction of the first proton beam is expected in 1998. The programs of use of the TESLA Accelerator Installation are: modification and analysis of physical properties of materials by ion beams, nuclear reactions with heavy ions at low and intermediate energies, radiation physics with light and heavy ions, radiolysis in condensed systems induced by light and heavy ions, physics of thin crystals, production of radionuclides and radiopharmaceuticals, and biological effects induced by irradiation with light and heavy ions.

The VINCY Cyclotron is optimized for the acceleration of heavy ions produced by an ECR heavy ion source, but it will have several windows for acceleration of H^-, D^-, H_2^+, and H_3^+ ions produced by a multicusp type light ion source, injected by a spiral inflector. These light ions will be extracted by stripping foil technique, resulting in proton beams in the energy range from 11-16, 22-36, and 60-70 MeV and deuteron beams in the energy range from 43-73 MeV.

The proton beams will be used for the routine production of ^{201}Tl, ^{111}In, ^{67}Ga, ^{123}I, and ^{18}F for medical purposes, using up to 50 % of total cyclotron beam time. The irradiation of the solid, liquid, and gaseous targets will be performed by automated target stations placed in a shielding vault separated from the other experimental channels of the installation. After the irradiation, the targets will be remotely transported into hot cells, for radiochemical processing.

The design of the solid target station will allow the irradiation of special targets prepared by electroplating for routine production of radionuclides (7° geometry, 1500 W beam power), as well as the irradiation of stacks of foils (90° geometry, 150 W beam power) for determination of excitation functions of nuclear reactions.

Discussion:

Q: T. Ruth: What beam current does this machine deliver?

A: It depends on the ion you are accelerating. For instance, for protons, as you have seen, we'll have several windows. The highest beam we have with low energy protons around 16 MeV and the current is a little bit below 50 μA. For high energy protons, that means around 70 MeV, we will have up to 2 μA. For other ions it depends mainly on the transmission of the machine and the ion source. For heavy ions, for instance C-12 we are expecting something like 5 μA.

Q: Who do you hope to supply with thallium, for example?

A: We are thinking just about the local market. We have something like 25 gamma cameras around Belgrade and we are going to supply them. That means something like 300 mCi per month.

Q: How do you control the position of the beam on your prototype during the irradiation? How do you control where the beam is during the production? The beam spot size on the target?

A: I wouldn't expect any problems, along the beam line you have a lot of focussing elements, quadropoles etc and the beam should be stable on the target. We are following the experience of other accelerator installations. And the beam is stable on the target for several weeks.

Q: R. Lambrecht: This very impressive what you have in your development but I'm a little bit surprised that you would choose Tb-149 as your first isotope, your beam currents are quite low. But leaving that aside, previous work from Australia and Geneva has shown that Tb-149 has only a 4.6 % positron emission that's not a very promising indication for PET.

A: You are quite right, the branching ratio is rather low and the current PET cameras can not use efficiently use that isotope. But we believe that we will have some development in PET cameras and in the near future we could use it.

Routine Production of [^{18}F]FDOPA by Automated Synthesis System

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National Institute for Longevity Sciences (NILS) was established in 1995 in Aichi prefecture, Japan for the purpose of conducting research in basic gerontology and geriatric disorders [1]. The Department of Biofunctional Research plays a role in NILS for elucidating the physiology, pathophysiology and biochemistry of aging and disease by the means of magnetoencephalography (MEG), magnetic resonance imaging (MRI) and positron emission tomography (PET).

L-3-(3,4-Dihydroxy-6-[^{18}F]fluorophenyl)-alanine ([^{18}F]FDOPA) has become one of the representative radiopharmaceuticals for PET [2]. In NILS [^{18}F]FDOPA scan of patients with degenerative disorders would be a major study protocol at present and in future.

We started to use this injection in September, 1996 and carried out eleven scans until January, 1997. The method we employed for the synthesis of [^{18}F]FDOPA is to fluorinate L-3-(3-hydroxy-4-pivaloyloxyphenyl)-alanine (4-*O*-pivaloyl-DOPA, a gift from Banyu Pharmaceutical, Japan) by [^{18}F]acetylhypofluorite followed by hydrolysis of the intermediate by 4M HCl and preparative HPLC (3, 4) This simple radiosynthesis enable six PET facilities in Japan to prepare [^{18}F]FDOPA.

The automated synthesis system provided by Sumitomo Heavy Industries consists of a reaction vessel made of glassy carbon, a vacuum pump for the removal of solvents and a preparative HPLC system. The whole system including targetry is monitored and operated by a personal computer (PC-9801, NEC, Japan). Typical time course representation of the synthesis was shown in Figure 1 and results were summarized in Table 1.

References:

[1] A. Igata, Arch. Gerontol. Geriatr. **19**: 203 (1994)
[2] A. Luxen, M. Guillaume, W.P. Melega et al., Nucl. Med. Biol. **19**: 149-158 (1992)
[3] K. Ishiwata,S.I. Ishii, M. Senda et al, Appl. Radiat. Isot. **44**: 755-759 (1993)
[4] K. Hatano, K. Ishiwata and T. Yanagisawa, Nucl. Med. Biol. **23**: 101 (1996)

Table 1: [^{18}F]FDOPA Production NILS

Cyclotron	CYPRIS HM-18 (Sumitomo Heavy Industries, Japan)
Target	0.3 % $^{19}F_2$ in Ne (84 μmol)
Irradiation	8 MeV deuteron 25 μA, 120 min (typically)
Recovery of 1 8F2	12.5 GBq at EOB under typical irradiation condition
Precursor for Synthesis	4-*O*-pivaloyl-DOPA (25 mg, Banyu Pharmaceutical, Japan)
Automated Synthesizer	CUPID (Sumitomo Heavy Industries, Japan)
Radiochemical Yield	6.0 ± 1.1 % (based on total produced ^{18}F with decay correction)
Specific Activity	39.6 ± 11.3 GBq/mmol (EOS)
Preparative HPLC	D-ODS-5-S5 120A column (ID20 X 250 mm, YMC, Japan) was used with sterile 0.1 % AcOH as eluent at 10 mL/min

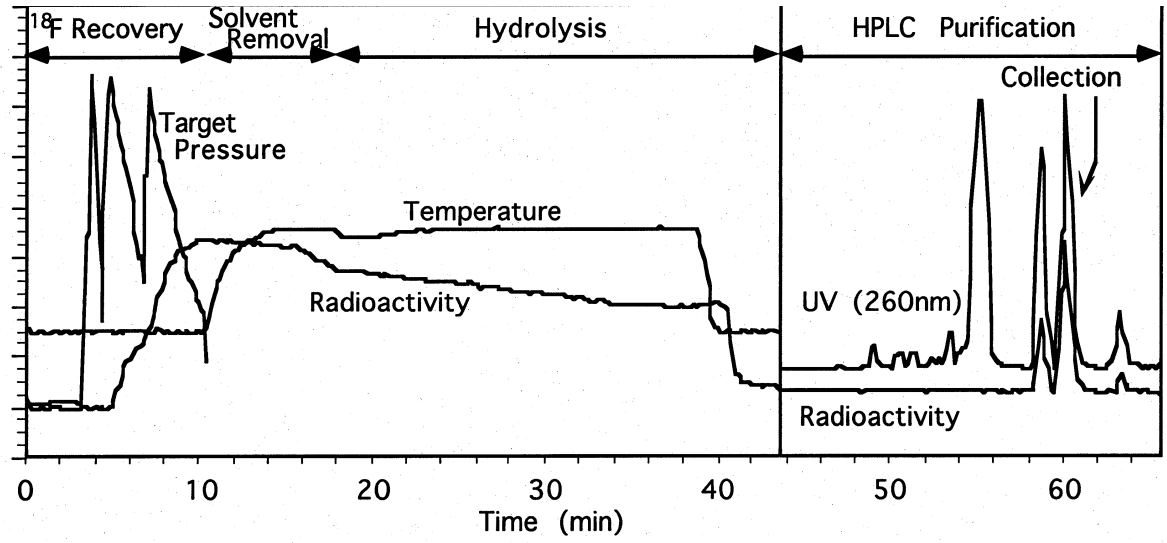

Fig. 1: Time Course of [^{18}F]DOPA Synthesis

Discussion:

Q: Tom Ruth: Have you considered using a destannylation reaction?

A: No. This method we describe is very clean compared to a stannyl or mercury reaction, for our impression.

High Yield Preparation of 6-[^{18}F]Fluoro-DOPA

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Because of the usefulness of 6-[^{18}F]fluoro-L-DOPA ([^{18}F]F-DOPA) for assessing dopamine metabolism, [^{18}F]F-DOPA is one of the standard PET radiopharmaceutica!s [1,2]. Despite enormous efforts a method which yields large amounts of [^{18}F]F-DOPA is not yet available [3,4].

Ours efforts aimed to improve the procedure of regioselective destannylation by Namavari et al. [3] to simplify the preparation and increase the yield. Since 1994 we have been producing [^{18}F]F-DOPA for research application. An apparatus for routine production based on electrophilic reaction was set up.

[^{18}F]F_2 is produced by the ^{20}Ne(d,α)^{18}F reaction, using the 13.5 MeV deuterons of the Rossendorf cyclotron U-120 with Ne + 0.2 % F_2 (100 µmol) as target gas. After EOB the [^{18}F]F_2-target gas is transported through a copper tube of about 500 m length to the radiochemical laboratory. To increase the efficiency of absorption, the [^{18}F]F_2 is absorbed in a special Vigreux absorption column containing a precursor solution of 60 mg N-formyl-3,4-di-boc-6-(trimethylstannyl)-L-DOPA ethyl ester in 15 mL trichlorofluoromethane. Under these conditions the reaction between the precursor and the gaseous [^{18}F]F_2 takes about 13 minutes. The volume of the solvent is reduced to about 5 mL by evaporation during absorption. After absorption of [^{18}F]F_2 2.5 mL 48 % HBr are added into the reaction vessel. The temperature is increased to 70 °C while the remaining solvent is evaporated by blowing in gaseous N_2. After evaporation the temperature is increased to 130 °C for 5 minutes to reach the conditions for hydrolysis. The product is purified on a HPLC column using an isotonic eluent (105.6 mM of CH_3COONa and CH_3COOH, pH 4.7). The main radioactive peak [^{18}F]F-DOPA) is eluated after about 11 minutes. The sterilization of the final product is achieved by sterile filtration of the eluent. The product has been characterized by HPLC, GC/MS, pH and Osmometer.

The total preparation time of [^{18}F]F-DOPA after EOB, including the radionuclide transport, takes about 50 minutes. The [^{18}F]F-DOPA yield relating to [^{18}F]F_2 is between 30 and 35 % (decay corrected) with good reproducibility. Starting from [^{18}F]F_2 a maximum yield of 50 % can be achieved due to the chemical background. So we were able to produce up to 1 GBq [^{18}F]F-DOPA starting with 4.5 GBq [^{18}F]F_2. The processing unit enables the [^{18}F]F-DOPA synthesis to be repeated twice without handling the processing unit in the hot cell. The pH value of the eluent plays an important role and should not exceed 5, othewise the final product is not stable enough and the color of the solution becomes light violet. The F-DOPA concentration was found to be between 1.5 and 2.5 µg/mL depending on the cold F_2-concentration of the target gas.

References:

[1] E.S. Garnett, G. Firnau and C. Namias, Nature **305**: 137 (1983)
[2] G.-J. Meyer, S.L. Waters, H.H. Coenen et alt, Eur. J. Nucl. Med. **22**: 1420 (1995)
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[4] J. Bergman, M. Hasparanta, P. Lehikoinen et alt, Tenth International Symposium on Radiopharmaceutical Chemistry, 476, Kyoto, Japan, 25.-28. October 1993

Discussion:

C: J. Clark: Just one thing that caught my eye: You are using Freon-11 as a solvent. Are these not been phased out rather rapidly?

A: Yes.

Q: J. Clark: Anyone in the audience who got a suitable alternative, a solvent that's going to be environmentally acceptable ?

A: G. Firnau: HF!

C: J. Clark: Günther Firnau is the HF protagonist as we've known for many years!

Q: G. Firnau: What is the amount in µmol of F_2 that you add to it?

A: We use about 100 µmol of F_2.

Production of 16a-[^{18}F]Fluoroestradiol in an Automated Module

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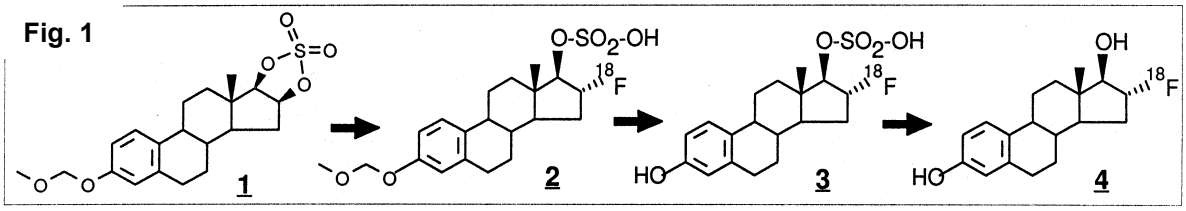
Based on a new synthesis procedure proposed by Lim et al [1] a rapid one-pot synthesis of 16α–[^{18}F]fluoroestradiol [2] has been elaborated with 3-O-methoxymethyl-16,17-O-sulfuryl-16-epiestriol (Fig. 1: 1) being the precursor. 3-O-Methoxymethyl-16α–[^{18}F]fluoroestradiol-17ß-sulfate (Fig. 1: 2) was obtained by nucleophilic substitution of 1 by n.c.a. [^{18}F]fluoride in refluxing absolute MeCN in the presence of Kryptofix 2.2.2 and K_2CO_3 within 15 min. A special hydrolysis procedure allowed 2 to be rapidly converted via 16α–[^{18}F]fluoroestradiol-17ß-sulfate (Fig. 1: 3) into 16α–[^{18}F]fluoroestradiol (Fig. 1: 4). After adding EtOH and using a subsequent RP-HPLC procedure, 4 was obtained in a 70 % overall radiochemical yield.

Fig. 1



The simple handling in the reaction route opened the possibility to transfer the procedure into an automated module. Instead of refluxing, the starting reaction mixture was heated in a closed bulb at 100 °C within 10 min. As hydrolysis medium 1 mL of a mixture of 1 M HCl:MeCN = 1:9 was used which was evaporated to dryness at 100 °C. This gentle process required 1 min and was repeated twice. The dry residue was dissolved in ethanol. Radioanalytic investigations of the ethanolic solution showed that in all cases 16α-[^{18}F]fluoroestradiol (4) was present as main product accompanied by a more polar, unknown radiolabelled product in about 6 - 10 % radiochemical yield which had to be separated. Up to now we have not succeeded in preventing this by-product by modifying the reaction conditions. The ethanolic solution was injected into an RP semi preparative HPLC system and eluted with 70 % aqueous EtOH as solvent. All by-products including the more polar, unknown radiolabelled one, Kryptofix 2.2.2, inorganic salts, and 16,17-O-sulfuryl-16-epiestriol formed from the excessive precursor were removed in this purification step.

The production of the title compound in an automated module followed by a semi preparative HPLC purification step required 50 min. The radiochemical yield of the fluoridation reaction was about 85 %, that of the hydrolysis step about 80 %. The total decay-corrected yield was about 70 %. We believe that the procedure in this form is suited for routine production.

References:

[1] J.L. Lim, M.S. Berridge and T.J. Tewson, J. Label. Compds. Radiopharm. **35**: 176 (1993)
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The UW Pelletron Lab: PET Radioisotope Production with the NEC 9SDH Tandem Accelerator

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Work is currently underway to expand and more fully integrate studies in functional brain imaging at the UW. Central to this effort is the need to provide oxygen-15, primarily in the form of [^{15}O]water, for quantitative cerebral blood flow imaging by PET.

Radioisotopes for PET at UW are currently produced using an 11 MeV CTI RDS 112 proton cyclotron located 3 miles across campus from the PET Imaging center. Although this arrangement has proven successful for the longer lived isotopes ^{18}F, ^{11}C and ^{13}N, the 2 minute half-live of ^{15}O requires a much closer proximity of the production site and scanner.

After considering various options for providing ^{15}O at UW, a 9SDH-2 Pelletron tandem accelerator from National Electrostatic Corporation [1] was ordered, to be sited near the PET scanner in a new Image Science Center. This machine is an ideal complement to the existing PET program, greatly enhancing radioisotope production capability as well as providing a versatile tool for studies of basis target physics and chemistry. Pelletron accelerators have been used successfully for production of medical radioisotopes in the past [2], and reliable ^{18}F production using the NEC 9SDH has recently been reported [3].

Advantages of this system include:
1. Well developed system technology. More than 120 NEC Pelletrons are currently in operation, used in a wide variety of applications including fundamental nuclear physics studies, semiconductor processing, PIXE material analysis, AMS, and freight security systems.
2. Ideal beam energy for ^{15}O production via the ^{14}N(d,n)^{15}O reaction.
3. Low cost relative to similar performance accelerators.

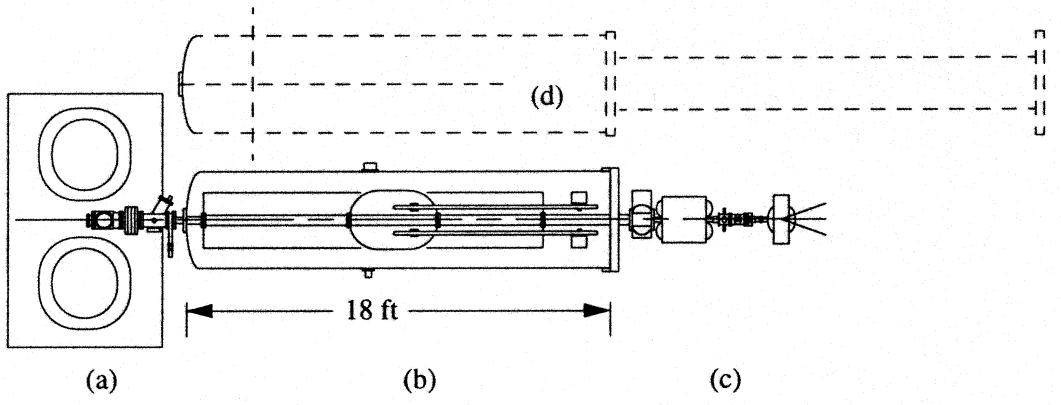

Fig. 1: NEC 9SDH-2 Pelletron accelerator in cross section. **a)** TORVIS ion source, **b)** acceleration tank, column, and single set of charging chains (300 μA maximum charge), **c)** high energy end pumping, quadropole magnet, beam diagnostics, fast beamline valve, dipole magnet, and three beam ports, **d)** tank service position (dashed lines).

The accelerator (Fig. 1), due for completion by June, 1997, will consist of a high current TORVIS ion source [4], 3MV tandem acceleration system, and high energy and focus and steering magnets. The beam is specified at 100 μA for 6 MeV deuterons (or protons) within a

1 cm diameter beam spot at one of three target ports. All target system component will be developed in-house.

References:

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David Schlyer, Brookhaven: Report on the Low Energy Accelerator Facility (LEAF)

Leaf came up because in the early 50‘s that whole facility was called LEAF, the Low Energy Accelerator Facility, the dynamiotron, the 18“ cyclotron, the 60“ cyclotron and the van de Graaf. All these accelerators taken together were called LEAF. So that’s where the name came from.

What we’ve got is a low energy, high current accelerator to play with. It has a beam energy of 4 MeV, a peak current of 8 mA and an average current of 100 µA. The repetition rate is about 100 Hz. The rationale for using this low energy accelerator is we could get it, and secondly what we are going to be doing with has a low energy, sort of worst-case scenario, in that we are right on the edge of the Bragg peak, so the dE/dx is higher. The accelerator can be upgraded at a later date, we are hoping to do that. We can make enough radioactivity to check production, although we cannot make enough to use it in routine operations.

This is what the accelerator looks like in our facility. We moved it into an existing vault where the small 3.5 MeV van de Graaf used to be. We also took advantage of a switching magnet they already had in place which allows us to split the beam plus or minus 50 degrees, so we can get at least 12 beam lines onto the machine. So this whole thing is built on a rack that sticks it up in the air at about 6‘ high.

This shows the back of the accelerator and then we have switching and quadrupoles in here to focus the magnet, and water-cooled slits so that we can very accurately define the energy for some other experiment we want to do.

This is what we have on there right now. We have a water target set up, ready to do irradiations on that, a prototype of the high current low energy water target, and this beam line over here is put on for studying BNCT, protons on lithium-7.

We had beam current through the machine just last week. It was actually delivered in April, but it took that long because of the regulatory problems we’ve had at Brookhaven.

A U. S. Department of Energy Virtual Isotope Center

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T.J. Ruth
Tri-University Meson Facility

L. Mausner
Brookhaven National Laboratory

For several years nuclear medicine professionals in North America have been exploring options to establish a long-term reliable supply of accelerator-produced research radionuclides. Much of the supply of these materials has depended upon the operation of large accelerator facilities by the U. S. Department of Energy (DOE). Since these accelerators operate primarily in support of nuclear physics research, the isotope production activity has been parasitic in nature and thus vulnerable to budget reductions in the nuclear physics funding entities. Furthermore, the operation schedules of these facilities have been driven by the physics research requirements and not by the needs of the researchers applying radioactive tracers. Therefore it has not been possible to assure reliable year-round supply in North America of some of the most promising short-lived radionuclides. Based upon input from a variety of interested constituencies a feasibility study was commissioned by the DOE to evaluate the construction of a U. S. National Biomedical Tracer Facility dedicated to the production, distribution, and development of medical applications of accelerator produced tracers. Upon completion of the study, it was concluded that the cost of construction of such a facility was too great unless it is clearly established that there is sufficiently high demand for the radiotracers in the biomedical and other research communities. In an effort to establish this, the DOE Office of Isotope Production and Distribution is now investigating the feasibility of using a distributed system of existing capabilities available in North America to cost-effectively meet the projected year-round demand for research radionuclides.

The combination of irradiation and processing facilities available among Brookhaven National Laboratory (BNL) in Brookhaven, New York, Los Alamos National Laboratory (LANL) in Los Alamos, New Mexico, and the Tri-University Meson Facility (TRIUMF) in Vancouver, Canada, could be used as a Virtual Isotope Center (VIC) to supply research radiotracers on a year-round basis. These three institutions have accelerator capabilities that could be coordinated in such a way as to activate targets to produce isotopes with half-lives as short as 48 hours, process the targets to recover the isotopes, and distribute them to the users on a year-round basis. LANL and Brookhaven possess excellent facilities and staff for both irradiating and processing targets to recover radioactive tracer isotopes. However, they are hampered by the lack of sufficient available beam time to produce the required radioisotopes on a year round basis. TRIUMF in Canada has beam time on its four cyclotrons to provide substantial irradiation services, but lacks adequate processing facilities. Thus the combined capabilities of these facilities could fill the demand for research radioisotope production throughout the year. TRIUMF would provide irradiation services during the year when LANL and BNL are not able to irradiate targets. The targets would be shipped to LANL or BNL for recovery and distribution of the research radiotracers. This work would be coordinated through the U. S. Department of Energy's Office of Isotope Production and Distribution (OIPD). The result would be a Virtual Isotope Center (VIC) that could supply the demand for research radiotracers to users on a year-round basis. The list of research nuclides that would be produced in this mode would be dictated by the interests of the biomedical research community and other interested research constituencies. We will describe the interest that

has been expressed to date, and as an example, we will detail our efforts to use the capabilities of all three facilities in a cooperative way to support clinical trials in the application of Cu-67 ($t_{1/2}$ = 2.580 days) to treat Human B-Cell Lymphomas at the University of California. We will discuss the issues related to compliance with the U. S. Food and Drug Administration regulations, scheduling of irradiations, shipment of radioactive targets, processing them to recover the Cu-67 according to user specifications, and shipping the Cu-67 product in a timely way to support the patient studies.

Discussion:

C: M. Welch: May I make a couple of comments? I'm wearing two different hats. I'm chairman of the Society of Nuclear Medicine Isotope Availability Committee. DOE showed the schedule recently for BNL and LANF that they will only be up for three months next fiscal year, so that's good, you can do lot of irradiations.

A: That's correct. Tom is going be busy.

C: M. Welch: And secondly, there is a mechanism in place for reviews of proposals. That is an advisory committee, that's my hat as a member of the advisory committee. Eckelman is chairman of the advisory committee that's going to review it.

C: J. Clark: Discussions on this rather ambitious virtual project which is a lot more than virtual, as far as I can see in terms of the hardware that's sitting out there ready to go.

V-48 Transmission Source Production

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Vanadium-48 ($t_{1/2}$ = 15.98 d) has been investigated as an alternative to Ge-68 for routine transmission scanning in PET. Prior work (Hichwa, et alt., NIMB 99 (1995) 804-806) has demonstrated the feasibility of routine production of V-48 using a titanium rod (> 99.99 % Ti, 73.7% Ti-48) and the $^{48}Ti(p,n)^{48}V$ reaction at energies available on many medical cyclotrons (incident proton energy = 17 MeV). Source strengths of 370 MBq (10 mCi) are produced from 20 μA irradiations for 120 min duration. Initial problems of variable linear source strength have been resolved by simultaneously measuring beam current at four locations along the Ti rod during bombardment. Irradiation times are adjusted at each location to compensate for fluctuations and eccentricities in beam profile. Each quarter of the rod receives 10 μA hr integrated current. Rod uniformity along the 10 cm active dimension is within 5%. Production runs are scheduled on Fridays. Short-lived radionuclidic contaminants decay during the 48 hr weekend period. Sources are used clinically for 7-10 days and then reirradiated.

Bill Lozowski, Bloomington: Report on International Nuclear Target Development Society

We are about 90 people who work primarily to solve the target problems of physics and chemistry basic research. We have several areas of interest in common with you, some of them are on this list. Others may not overlap at all. Most of these have to do with preparation of thin films of separated isotopes which historically has been the usual work of about 70 % of us.

Why did we become an organization? We trace our roots to 1963 and the First Symposium on Research Materials Nuclear Measurements. There were three of these symposia before the first official INTDS conference in 1972. In 1984 we went from a yearly conference schedule to a biannual one. Since 1984, the conference site has alternated between Europe and North America. The Proceedings have been published as a special issue of Nuclear Instruments and Methods which makes them nicely available to everyone. The meetings of ’63 and ’73 did not produce proceedings, but the rest did.

How do we get all that information? In 1992 we gained a computer database, an index to it. This article from NIM -A, 334 (1993) describes the database and also has a better history of our society.

Today more than 700 articles have been indexed with keywords from a list of 241. The names of the chemical elements were chosen as keywords and I’ve listed some others here that may point to articles useful to those of you here. We call it our database because it started out as a true computer database in Paradox 3.5, but the current form is Microsoft Excel file. That is easier to convert to your favorite format or simply load it into a word processor as an ASCII file, and the word search is on the keywords. It’s available from the editor of our newsletter, Chris Ingelbrecht. The newsletter is published twice a year, the format is intentionally informal, usually the contributions are just photocopied and printed. The content is just what you would expect, the directory of members in addition to mailing addresses has phone and fax numbers and most of us have email addresses so we can get back to you very quickly.

We are incorporated in California as a not-for-profit organization. Our corresponding secretary and treasurer handles membership. The dues are $50 for two years, and that entitles one to a copy of the proceedings whether one attends the conference or not, four issues of the newsletter, a reduced conference fee and voting privileges.

In the fall of '98 our 19th World Conference will be hosted by Oak Ridge National Lab, they have wonderful facilities there, we've been there before, the nearby Smokey Mountain National Park is really nice in the fall. In 2000, for our 20th, we'll return to Gale, the place where it all began for us in 1963. I hope that some of you can attend one or both of these meetings. Probably what you should do is get our database and look through it and see what we are about. But I can tell you that we are broad spectrum target makers, we cover things from reference samples of powdered fish to accelerator targets of natural diamond and you'll even learn how to explosively clad them if you like.

Discussion:

J. Clark: Are there any immediate questions for Bill ? Tom would like to make a few comments from the floor after that. With all the details you've seen on the slides you want to make your internet available.

C: T. Ruth: It was last fall, at Strassbourg, Frank Helus and myself and Jean-Luc Morelle and a couple of other people attended the meeting with the idea that should we get the two organizations closer together even though theirs is a formal organization and ours is anything but formal. But from that meeting there is definitely overlaps that would be of great interest to many people here. However it's going to be a fairly narrow overlap because they are used to dealing with targets in the nanoA region and very thin foils whereas we are dealing with very high beam currents. But there are techniques that are definitely overlapping, so I think in fall of '98 when it's at Oak Ridge I really impress upon those of you who are in North America to attend the conference. Anyone in the world can attend, but Oak Ridge is obviously very convenient for the North Americans and Belgium is convenient for the Europeans and others to attend. I think, take the opportunity to talk to Bill about what they're doing and we'll see where it goes from here.

Germanium-68 Problem Progress

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M.A. Kozlova, G.E. Kodina and **A.B. Malinin**
Institute of Biophysics, Moscow, Russia

As we have noted at the last workshop [1] the ^{68}Ge - ^{68}Ga generator system is in our opinion one of the perspective systems for the production of the short-life radionuclides for PET. And this explains our great interest to the germanium-68 production and its applications.

Considerable attention is given to the improvement of ^{68}Ge-radionuclide production. Several problems are here: a decrease of ^{66}Ge-losses, a search of new extractants, a decrease the final volume of the product to increase a volume concentration activity. The latest is important for some applications.

Now we have three extractants for ^{68}Ge-separation from the irradiated targets. Each of them has their advantages and disadvantages. It is important that technologies using different extractants are carried out on the same simple plant shown in Figure 1.

Many users do not need germnanium-68 in the solution but they want to have different products with this radionuclide. Therefore we work also in this direction.

We have developed a line source with 68-Ge for medical Positron Emission Tomograph (PET) checking recently. An active area of this source is a wire near 1 mm in diameter and not less than 110 mm long. The source is shown in Figure 2. Standard deviation for sources with 15 mCi of ^{68}Ge is loss than 1.5 %. The developed technique allows to make sources over a wide range of length.

In our opinion PET-centers have interest to ^{68}Ge /^{68}Ga-generator. Many articles concerning to this question are published, as example [2-4]. We using preceding experience [5] prepared three generator with the ^{68}Ge-activity from 1 to 25 mCi. The generator is shown in Figure 3. The device allows to have ^{68}Ga at any time. As an eluent we used 0.1 M HCl. In all cases the ^{68}Ga-yield in 5 mL of the eluate was not less than 60 % in the first time of the operation.

The breakthrough of ^{68}Ge was not more than 5 x 10^{-3} %. During operation the ^{68}Ga-yield is decreased gradually. Now our activities are directed to increase the ^{68}Ga-yield and to solve some other problems.

References:

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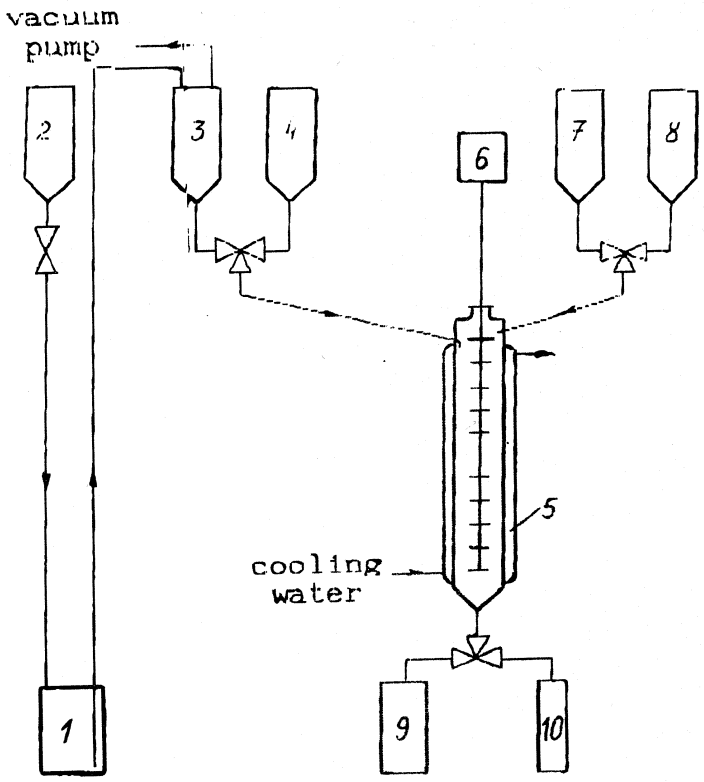

Fig. 1: The installation for germanium-68 separation. **1)** flask for shaving dissolution, **2,4,7,8)** vessel for technological solutions, **3)** intermediate vessel for initial solution, **5)** extractor with cooling “shirt”, **6)** stirrer, **9)** flask for waste, **10)** product receiver.

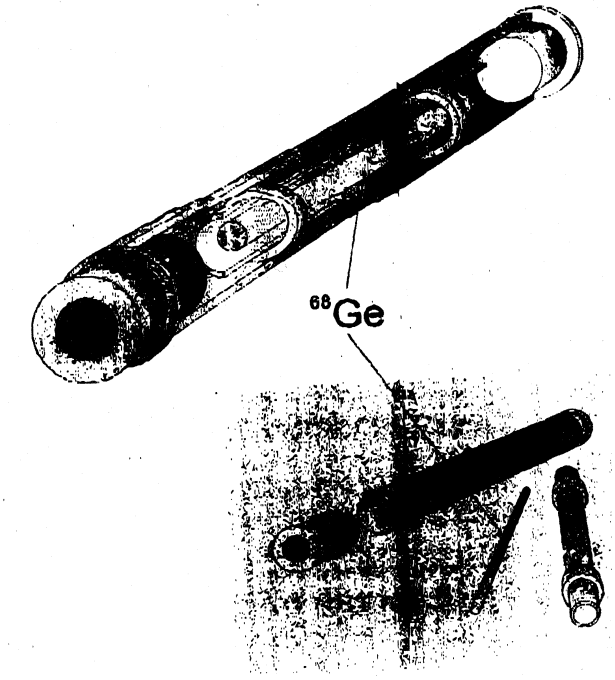

Fig. 2: The line source for PET checking.

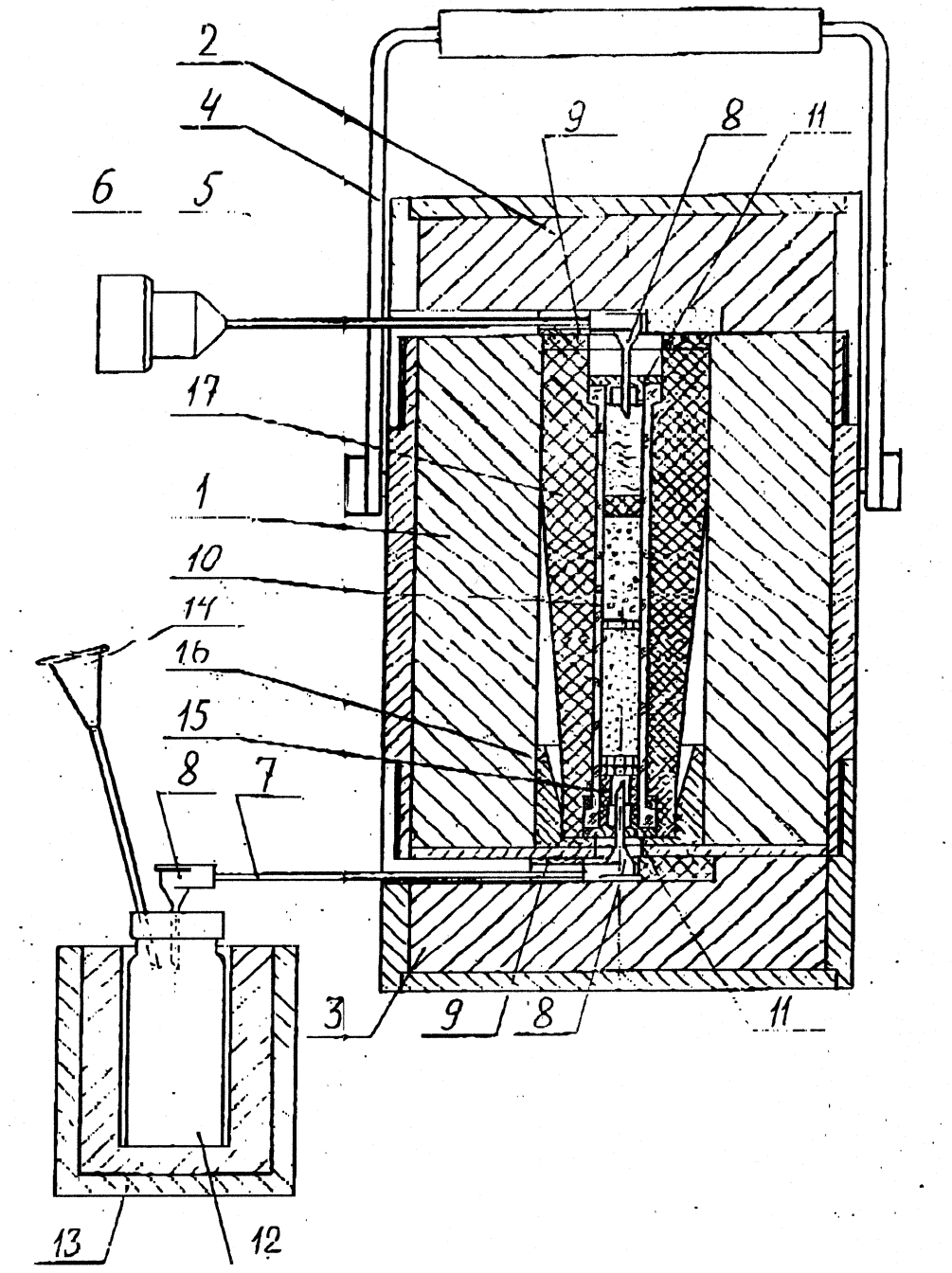

Fig. 3: Scheme of ^{68}Ge/ ^{68}Ga – generator:

1) container body
2) upper cover
3) lower cover
4) handle
5) eluent line
6) funnel
7) eluate line
8) corner needle
9) stop
10) generator column
11) column cork
12) eluate vial
13) shielding container for eluate
14) air needle
15) preservative ring
16) rubber inset
17) column holder

Design and Operation of a Krypton-82 Gas Target for the Regular High Yield Production of Rubidium-81 for the Preparation of Krypton-81m Generators

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The gaseous daughter of rubidium-81 ($t_{1/2}$ = 4.58 h), krypton-81m ($t_{1/2}$ = 13.3 s), has been used for many years as a valuable radiopharmaceutical for imaging regional lung ventilation. Since September 1975 the MRC Cyclotron Unit has supplied krypton-81m generators to several nuclear medicine departments within the UK, to the extent that this is now the second most popular radiopharmaceutical in UK nuclear medicine.

Historically, we have produced rubidium-81 by the (α,2n) reaction on bromine-79, using a target of natural sodium bromide fused onto a reduced copper plate. There are several disadvantages with this method, including difficult target preparation, the need to store used radioactive copper target plates, the need to process the target after irradiation and the production of unwanted radioisotopes of rubidium (typically 20 – 25 %) which contribute significantly to the surface dose and 'transport index' of the container. The possibility to produce rubidium-81 from gaseous krypton-82 by the (p,2n) reaction [1] is attractive because the method can be easily automated without many of the disadvantages of the sodium bromide route. When a Scanditronix MC40 cyclotron was installed in the our Unit in 1985-7, a beam line dedicated to this method of production was included in the design. We therefore investigated the design and operation of new targets for this process.

The engineering aims were to produce a reliable and maintainable system, using where possible equipment and parts already in use within the Unit. Target windows were to be of designs already proven on other targets. The operating pressure of the target was to be kept at moderate levels (50 - 100 psig) and all the equipment in the cyclotron vault, apart from the target, was mounted on a trolley to allow its removal for fault-finding and maintenance. Control was by a programmable logic controller (PLC) mounted outside the vault with a test connector so the trolley control lead could be plugged in for testing. The main controls for both vacuum and pressure were mechanical gauges with electrical contacts with more precise control and monitoring being provided by electronic gauges. Nupro valves were chosen as these have a switch to positively detect operation of the valve.

An interesting engineering detail was that the mechanical gauges were not compatible with the PLC inputs due to the low current from the PLC input. A repeater relay was necessary to boost the current in the gauge contacts!

A target with a 25 mm front window and an internal volume of 190 mL was investigated initially. Beam energy and current were optimized by irradiations of natural krypton gas. Automatic sequences were developed for the target loading and unloading cycles. The load cycle evacuates the target and then pressurizes it with the target gas and the unload cycle cryopumps the unconverted gas back into the gas reservoir using liquid nitrogen as the coolant. Wet steam washes the rubidium-81 from the walls of the target and transfers the resultant solution to the hot-cell ready to load the rubidium-81 directly onto the generator columns. Estimates were made of the yield both in terms of rubidium-81 and the other rubidium isotopes, as a function of the proton energy and target pressure. The results were broadly in agreement with published data [1].

Estimates of the efficiency of the cryopumping can be obtained by monitoring the change of krypton pressure with time. However a direct readout of the ultimate cryopumping pressure was required for both analyzing the effect of alterations during the development phase and for performance monitoring during routine production. The vapor pressure of krypton at liquid nitrogen boiling point (77.3 °K) is of the order of 4 mbar. This lies between the ranges for mechanical and pirani gauges. An absolute pressure gauge using a piezoelectric pressure sensor was found with the range 0 to 1000 mbar in 0.1 mbar steps.

Based on these results, a new nickel-plated aluminum target (volume, ~ 40 mL) based on a previously used design, was manufactured. A sectional view is shown below (Figure 1). Internally, the target is a conic section with a 10 mm diameter window at the front, 20 mm diameter at the rear and length 200 mm. Incorporated in the target body are drillings for water cooling. The back plate of the target is also water-cooled and this acts as a beam dump. The target window (0.7 m aluminum) is cooled using a helium double foil assembly. All O-ring seals are Viton. This target is capable of operating at a gas pressure of 200 psig.

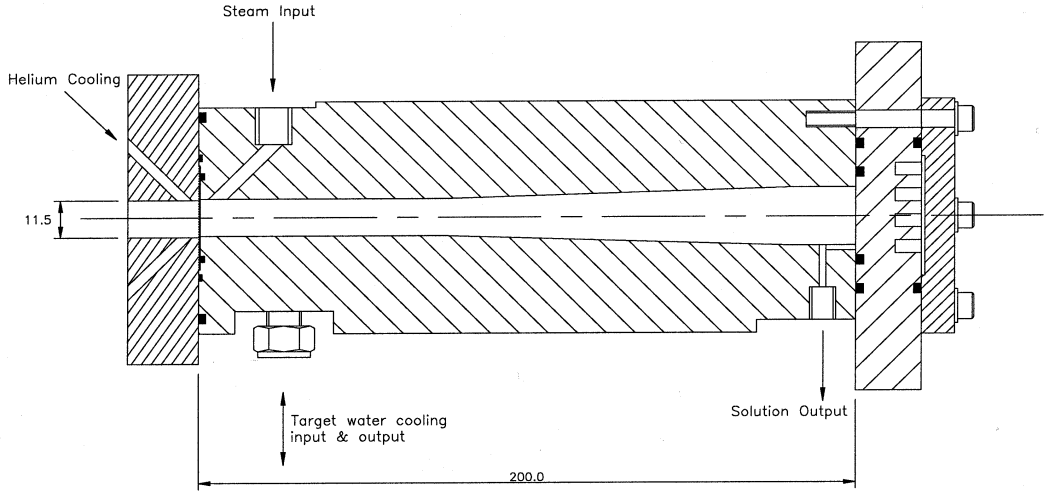

Fig. 1: Target Cross Section

Testing continued using krypton-82-enriched gas (> 90 atom %). The combination of the new target design and the krypton-82-enriched gas, as expected, gave further improvements in both yield of rubidium-81 and reduced levels of unwanted rubidium isotopes. At a target pressure of 70 psig, the incident beam energy was 30 MeV and the target current at 30 µA. Operating at a relatively low pressure significantly reduces the stress on the target window. It is estimated that the incident beam energy is degraded to about 27 MeV by the double foil unit and about 6 MeV is dropped in the gas, with 21 MeV in the beam dump. The published data indicates that we could, if required, increase the pressure, to drop only 18 MeV in the beam dump. Beyond this the yield of rubidium-81falls off while the yield of the unwanted rubidium-82m continues to rise.

Typically, the level of rubidium-82m, the principal contaminant, was reduced to less than 9 % of the total activity, and the surface dose/transport index reduced by a factor > 2, when compared to an equivalent generator prepared by the sodium bromide route. The production rate, corrected to the end of bombardment, is about 10 GBq/h. About 7-8 generators per hour can be produced by this route compared to 2.5 by the sodium bromide route. A standard MRC generator produced by this route has an activity of 650-750 MBq at 0900 hrs on the day used by the customer. We are currently supplying about 50 % of the generators used in the UK. This is typically 50 generators which corresponds to an estimated 300

patient studies. The recovery of the precious krypton-82 gas, for reuse, is highly reliable and efficient.

The system to recycle the target gas, steam the target and transport the solution to a hot cell for loading onto the generator columns is illustrated below (Figure 2). All the critical areas use stainless steel piping and "Swagelok" fittings.

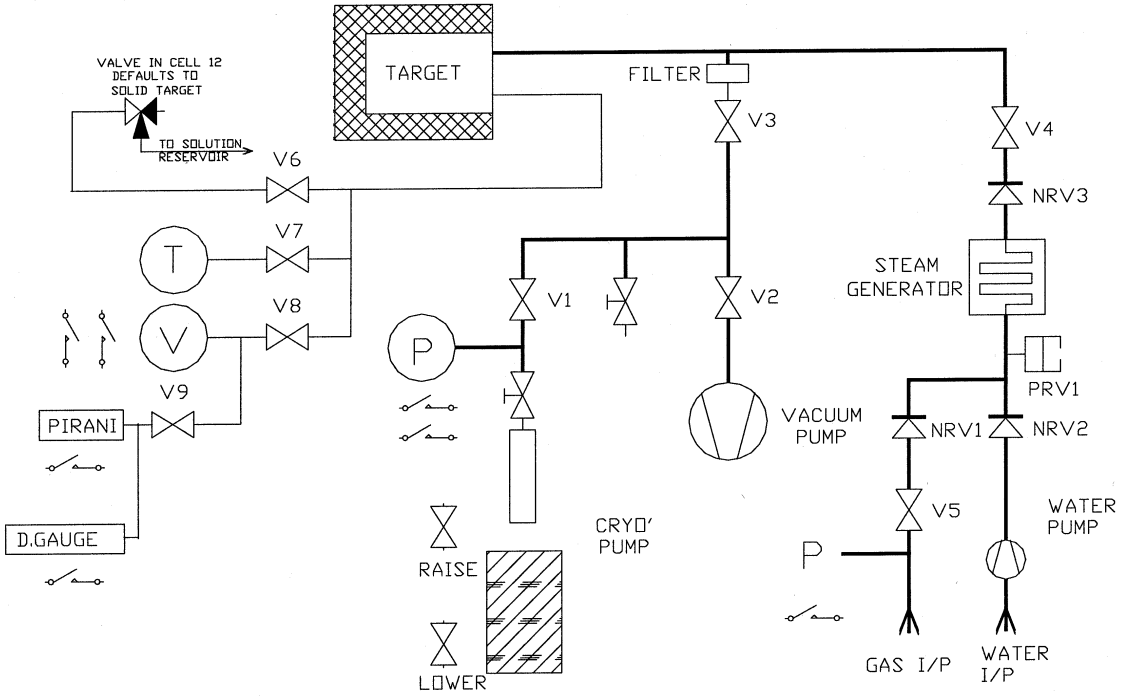

Fig. 2: Target Plumbing Diagram

The operafing sequence is as follows:
CHECKS

1) Krypton pressure in reservoir
2) Sufficient water for steaming
3) Gas cylinder for target emptying
4) Fill cryogenic dewar with liquid nitrogen

TARGET LOAD SEQUENCE

1) Rotary pump on (ff off) and valves V2 and V3 open and after delay V8 opens.
2) Valve V9 opens after mechanical gauge has been below low detection (-25 inches Hg) for 2 seconds.
3) Wait for Pirani detection ($2xl0^{-1}$ mbar) then close valves V9 and V2
4) Open valve V1 and close once mechanical gauge has reached high pressure detection (70 psig)
5) Close valve V3 and send ready signal to cyclotron control system; V8 remains open.

TARGET UNLOAD SEQUENCE

1) Stop target ready signal and turn on heaters for steam generator and target body
2) Raise cryogenic dewer slowly to cool "pump"/reservoir
3) Detect cooling by reservoir pressure falling to 0 psig then after short delay valves V2 and V3 open and detected
4) Valve V9 opens after mechanical gauge has been below low detection for 2 secs.
5) Wait for absolute pressure diaphragm gauge detection (19 mbar)
6) After a delay ALL valves close and "blow out" signal sent to target cooling.

7) Open V4 and V5 for short time to relieve target vacuum
8) Wait for steam generator to reach temperature and "blowout" complete.
9) Open V6 and V4 and send ready signal to hot cell
10) Start water pump to inject steam for preset time
11) Stop water pump and open V5 to empty target to cell using helium at 50 psig
12) After 9 mins close all valves and stop steam generator heater
13) Valves V2 and V3 open and rotary pump and target heater runs for one hour
14) Heat off and target remains pumping until next load cycle

The enriched krypton gas target route and automated target load/unload facility meet all of the MRC's current requirements for krypton-81m generator production and give considerable scope for increasing production rate in the future.

Reference:

[1] Z. Kovacs, F. Tarkanyi, S. Qaim and G. Stöcklin, Excitation-functions for the Formation of some Radioisotopes of Rubidium in Proton-induced Nuclear-Reactions on Kr-Nat, Kr-82 and Kr-83 with Special Reference to the Production of Rb-81(Kr-81M) Generator Radionuclide, Appl. Radiat. Isot. **42**: 329-335 (1991)

Ten Years Experience with a Heavily Used Target for the Production of [^{18}F]Fluoride by Proton Bombardment of [^{18}O]Water

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Introduction

Our original target for the regular production of [^{18}F]fluoride by proton irradiation of [^{18}O]enriched water was built during 1987 and 1988 [1,2]. The construction of the target is detailed in Figure 1. The target has a metal cavity (25 mm diameter, 3 mm depth), composed of a 316 stainless steel insert with metal to metal seals to the front (0.5 mm aluminum-0.025 mm titanium) and back foils (0.025 mm titanium-2 mm aluminum). The front foil is cooled with helium and the back foil with chilled water. The target operates at low pressure with 1.5 mL of ^{18}O-enriched water, loaded as required from a reservoir in close proximity. Water lost from the cavity, as a result of boiling and radiolysis, is recirculated. Originally, palladium was present in the head-space to catalyse recombination of oxygen and hydrogen. The target has to be unloaded to a hot-cell 40 m distant. The [^{18}F]fluoride is mainly used for the regular production of 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG). Over the last 10 years several changes have had to be made to the target system, its operation and maintenance to improve reliability and performance. This experience and these changes are summarized here.

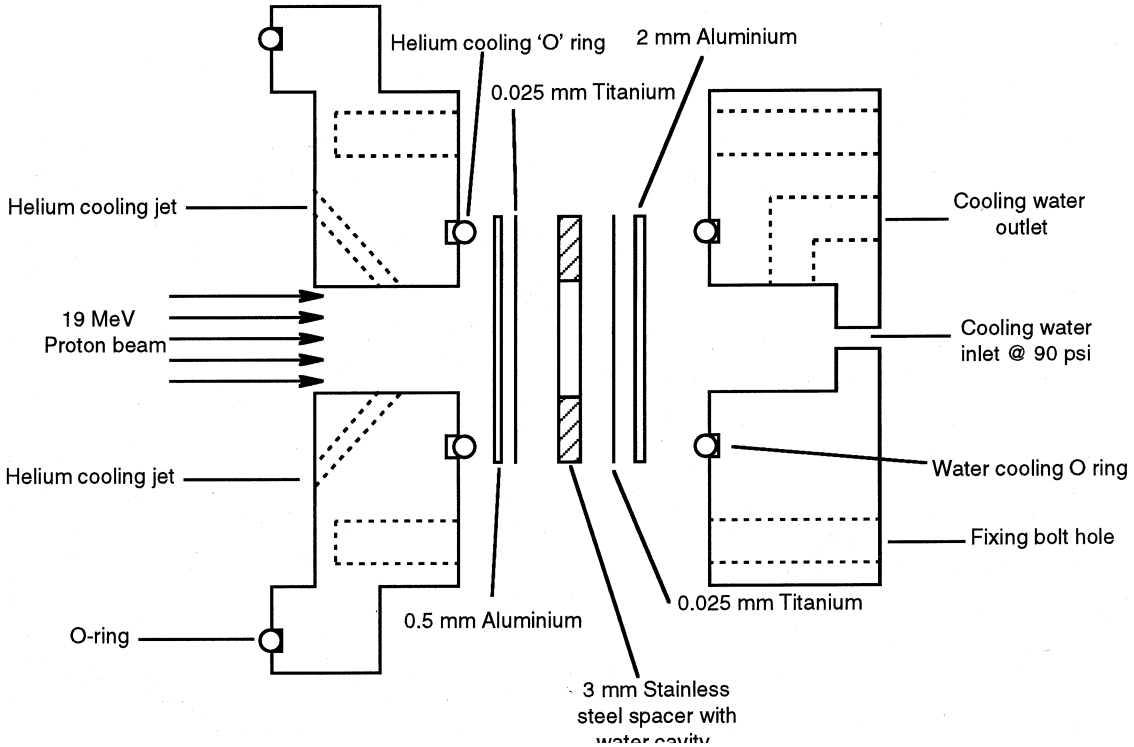

Fig. 1: An exploded schematic view of the target in use at the MRC Cyclotron Unit for [^{18}F]fluoride production (adapted from references [1] and [2]).

A. Alterations Made to Ensure Reliable [^{18}F]Fluoride Target Performance

During heavy repetitive use of the target system over long periods, many unforeseen problems arose which required various actions for short or long-term solution. These are detailed in chronological order in Panel A.

Panel A: Problems arising in the use of the target and actions taken

Problem	Action
Microbore (1/32"o.d.) polyethylene emptying tubes blocked after single use.	Tubes replaced with Teflon tubes (1/16" o.d.).
Glass catalyst reservoirs leaked during bombardment.	Replaced with pressure-tight stainless steel versions.
Low yields due to 'growth' of pyrogenic material in ^{18}O-enriched water reservoirs.	Sterile conditions developed (see below).
Poor control and reliability.	Programmable logic controller added.
Emptying problems due to water 'breaking up' in tubes.	Installed a GC mass controller to 'smooth out' gas flow to the target.
Emptying problems caused by a build up of drips in emptying tubes.	Started weekly cleaning and drying of lines with ethanol-dry nitrogen (see below).
Target failure due to radiation damage of flow controller.	Suitable replacement unavailable.
Filling-rig failure due to non-radiation resistant components.	Replaced with metallic-pneumatic syringe drive system.
Radiation damage of plastic components.	Started weekly target checks and annual replacement of damaged items (see below).
Purchased contaminated ^{18}O-enriched water (during world shortage), resulting in low yields, emptying difficulties and poor radiochemistry.	Attempted purification of water by fractional distillation (see below).
Poor emptying of target.	Gas control system rebuilt and tested for 6 months before introduction into routine use. System still in use.
[^{18}F]Fluoride sticking to palladium catalyst.	Catalyst removed with no effect on yield.
Radiation damage to Teflon tubes.	Replaced Teflon with more radiation resistant polypropylene tubes.
Possible contamination of [^{18}F]fluoride from plastic components used in target filling system	Reprogram target filling rig to reduce contact time between ^{18}O-ennched water and plastic components.
Target yields variable and possible contamination of [^{18}F]fluoride.	Varied target foils and bombardment conditions to improve yield.
Irradiation of cooling water, producing copious nitrogen-13.	Thickness of aluminum back foil was increased.

B. Investigation of Water Transfer

The transfer of ^{18}O-enriched water through 40 m of 1/16" o.d. tubing was studied using a model target system set up in the laboratory. Colored water was used to simulate ^{18}O-enriched water and to aid observations.

A single slug of water was easily able to pass through the tubing. In this case, the transfer gas pressure only has to overcome 2 components due to surface tension acting at the two liquid-air interfaces *i.e.*

$$P > F_1 + F_2$$

(where P is the force required to move the water through the tubing and F~ and F2 are the two components due to surface tension).

It was found that with less controlled target emptying, the slug of water was broken into 2 or 3 segments. The more segments, the slower was the transfer through the tubing. A higher gas pressure was required. Obviously, with even more segments of water, there is a greater number of components (due to surface tension) that the transfer gas pressure has to overcome *i.e.* for n components.

$$P > F_1 + F_2 + F_3 + F_4 + ...F_n$$

At higher pressures, the back end of the slug tended to break up leaving a small number of drips in the tubing. This effect was also seen when contaminated ^{18}O-enriched water was used or when cleaning solvents had not been completely removed from the tubing. Once drips were present in the tubing, a slug of water tended to break up into segments, even when slow controlled transfer conditions were used. When the number of segments in the tubing became too great, the transfer gas pressure was insufficient to overcome the surface tension of the combined segments. In this case, compression was seen.

When the water slug was broken into many segments, increasing the transfer gas pressure only squeezed the segments closer together rather than continuing to push the water through the tubing. If extreme pressure was used to force the water through the tubing, a fine coating of small drips was left behind. Subsequent slugs of water would not pass through the tubing without severe segmenting. Further drying of the line did not remove these effectively. The only solution to remove the drips was to wash the lines with a suitable solvent and then dry the lines with air.

Another effect was seen when the previous emptying process was incomplete *(i.e.* water was left behind in the tubing). A slug of water from the current 'empty' could displace a slug of water from the previous 'empty'. At the end of the empty cycle, it would be the slug of water from the previous 'empty' that would arrive at the cell with the slug from the current empty remaining in the tube. In this case, it would appear that the target had emptied, but in reality, the radioactivity would be stuck in the lines, implying that there had been a target failure rather than an emptying fault.

Once a build up of drips and emptying failures had occurred,-the problem only got worse. Only by cleaning the lines could the empty cycle be returned to its correct operation. If the level of ^{18}O-enriched water in the reservoir was allowed to rise above the level of the delivery tube, capillary rise occurred, 'sucking' contaminated water back into the tubing. Once the water had traveled to the point where the tubing traveled under the laboratory floor, syphoning occurred. The target empty lines could potentially 'fill' themselves with several milliliteres of recovered enriched water. The following target empty would then fail.

C. Experience of the Purification of ^{18}O-Enriched Water by Distillation

^{18}O-Enriched water, recovered from [^{18}F]fluoride, after passage through an AG-1-X8 column in carbonate form [3], can become contaminated with amine residues from the resin. Fractional distillation of the recovered ^{18}O-enriched water gives two fractions. Fraction 1 (85-90 °C) is a colourless volatile liquid with a strong, sweet odour. Fraction 2 (100 °C) is the ^{18}O-enriched water but it still retains a strong odour of Fraction 1 after distillation. This implied that the impurity was not separated effectively from the ^{18}O-enriched water. Re-distillation from potassium permanganate and potassium hydroxide [2] did not improve the purity of the water. In this case, the oxygen-18 enrichment level after distillation was found to be lower than after 'normal' distillation. After 2 - 3 distillations, build up of Fraction 1 in the ^{18}O-enriched water was significant. After 2 - 3 weeks use, the light organic material was found to

cause the break up of ^{18}O-enriched water in the target empty lines. Currently, irradiated ^{18}O-enriched water is not recycled for reuse.

D. Development of Maintenance Protocol

Heavy use of this target over this period (several irradiations per week) has also required a maintenance protocol (Panel B) to be evolved and implemented to combat various problems arising, many of which are mentioned in Panel A.

Panel B. Current maintenance programme.

Weekly:-	Visual check for damaged or kinked lines Leak test Fresh ^{18}O-enriched water prepared for one week's use Empty lines flushed with gas
Monthly:-	Plastic components tested for radiation damage Valves tested for correct operation Target pressures checked Empty lines cleaned and dried (with solvents and gas) Radioactivity yield checked from standard irradiation
Biannually/Annually: (depending on use)	Target stripped/cleaned All foils replaced All plastic components replaced Empty lines checked for damage Rebuilt-target leak tested on bench
Maintenance of sterile conditions: - Refrigerated storage of ^{18}O-enriched water. - Use of new sterile needles/transfer syringes every week. - Sterile, dry, nitrogen filled vials used as reservoir. - New reservoir prepared every week (filled with sufficient ^{18}O-enriched water for one weeks use). - Sterile filter used on reservoir vent.	

Panel C. Current operation and performance parameters of improved target

Pressure	2.5 bar
Beam current	20 μA
Proton energy (incident)	19 MeV
Proton energy (cavity)	16 MeV
Best yield	990 mCi at EOB (60 min irradiation)
Average yield	350-500 mCi at EOB(30 min irradiation)
^{18}F Production rate	50-60 mCi/~Ah at EOB
Specific radioactivity	150 Ci/μmol at EOB (determined by measurements on FDG)

Discussion

With the alterations (Panel A) and the maintenance protocol (Panel B) in place, the target performe well with respect to yield and reliability (Panel C). High specific radioactivity is routinely obtained as verified by measurements on FDG and other compounds labelled with this source of [^{18}F]fluoride. Some other reactions of the [^{18}F]fluoride *(e.g.* with diaryliodonium salts; [4]) seem sensitive to occasional chemical contamination of the irradiated [^{18}O]water, as indicated by perturbed chromatography of the [^{18}F]fluoride on reverse phase HPLC. This phenomenon is being investigated further with a view to avoiding contamination and developing quality assurance for the chemical purity of the irradiated product.

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A Convenient Semi-Automated System for Optimizing the Recovery of Aqueous [^{18}F]Fluoride from Target

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Centres with a heavy load of patients undergoing examination and that use [^{18}O]H_2O of a low enrichment grade as target material have a strong requirement not to waste any of the activity produced. More over, it is not unusual in a PET laboratory the need to split the target activity in order to carry out more experiments with just one load of expensive [^{18}O]H_2O. On the other hand this operation is somewhat more demanding when the bombardment is of large entity. To take out, in an automated or remote-controlled way, a few mCis from a batch of 600 or more is not an easy task, especially when one considers the small volume of carbonate solution (315 µL in our own procedure) on which the [^{18}F]fluoride is dissolved after elution from the Dowex 1X8. Besides, the presence of carbonate in the aliquot could be undesirable to the intended use. To cope with all that we developed a convenient semi automated system whose simplified drawing is shown in Fig. 1.

The apparatus, which includes a [^{18}F]fluoride/[^{18}O]H_2O recovery set-up similar in part to that previously described in literature [1], is integrated with the pre-existing Liquid Target Fill (LTF) unit (Scanditronix Medical, Sweden). The latter allows to control the target loading/emptying operations from a console placed in the hot-lab and to monitor the target pressure during the bombardment.

[^{18}F]fluoride recovery
Briefly, at the end of bombardment the target content (780 µL) was transferred remotely via He-pressure (2 bar) throughout a 16-meter-long teflon tube (0.5 mm i.d.) to the separation unit, which involves a pneumatically-operated 6-way injector valve (Inj.V) and a 3-way slider valve (V7). To avoid any possible release of volatile activity *(e.g.* [^{13}N]NH_3, [^{13}N]N_2 [^{13}N]NO_X) the vacuum line was channeled into a 100-meter-long delaying pipe (12.7 mm i.d.) which makes up our Gas Waste Storage System. As trapping column we used a commercial guard column with 20 x 2.1 mm i.d. stainless steel cartridge (sample clean-up column, Hewlett Packard) full loaded with *ca.* 36 mg of Dowex 1X8 ($CO_3^=$). Once loaded, the resin was washed with *ca.* 1 mL of deionized water, and next flushed for 30 min. with nitrogen flow.

To be on the safe side, unloading of the target was allowed for 140 s even though 100÷120 s were generally enough to have a stable reading of the activity trapped in the guard column. Trapping efficiencies of [^{18}F]fluoride were typically above 99.9 %. Elution of the trapped activity was done, after switching Inj.V and V7, with 0.11 M K_2CO_3 (315 µL) previously loaded in the loop. Recovery efficiencies were usually well above 99 %.

Sorting of the activity
Basically, after [^{18}F]fluoride trapping, the system permit the rinsing of the transport line by opening for a pre-set time V8 (V1 was already open from the previous target unloading operation) to allow a reasonable amount of deionized sterile water to flush throughout the transport line up to the hot-cell.

Recovery of [^{18}F]fluoride/[^{18}O]H_2O and rinsing sequence are both integrated into the RB-86 robotic system operating program (Anatech, Sweden) used for [^{18}F]FDG synthesis. Therefore, after [^{18}F]fluoride has been trapped on the Dowex 1X8 ($CO_3^=$) resin, a message on the PC screen allows the operator to choose between the following options:

- skip the washing sequence and continue with [^{18}F]FDG synthesis. The [^{18}F]fluoride retained on the column is washed off the resin with K_2CO_3 solution into the reaction vial;
- direct the washing to the resin in order to increase the amount of activity at SOS. In this case V6 is activated to divert the eluted from the guard column to the waste in order to avoid the isotopic dilution of the[^{18}O]H_2O previously recovered. When the radiodetector placed in proximity of the guard column does not signal any further increase of trapped activity (typically, after 60÷110 s) a command is given from the PC keyboard[1] to close V6 and proceed with the following step, i.e. the [^{18}F]fluoride elution with K_2CO_3;
- collect the washing for other tasks, such as research chemistry, PET-camera calibration and skeletal investigations by PET. In this case V5 is switched for 110 s after which the [^{18}F]fluoride elution step with potassium carbonate solution takes place.

Results and discussion

One difference in our system, when compared with other described in literature [2] is the choice of excluding the target cavity from the washing operation. In our opinion this approach offers a two-fold advantage:

1. the system conditioning for the following run, namely the removing of any residual deionized water which would otherwise affect the isotopic integrity of the [^{18}O]H_2O to be recovered, is made much faster;
2. as no deionized water ever passed through the target it ensures consistency in the enrichment grade of the bombarded [^{18}O]H_2O, a critical factor in assessing the quality of a target by its saturation yield value.

Besides, periodical or emergency cleansing of the target cavity can still be executed in our case by selecting the second reservoir (H_2O) of the LTF unit.

An indirect confirm to the validity of this approach comes from the measurement, by mass spectrometry, of the percentage of oxygen-18 in the recovered water after resin, which was found to be 94 % against the 98 % originally loaded in the target. This loss is comparable to the one reported by other authors [3] who, however, used a larger volume of irradiated water (2-3 mL) and consequently suffered from a smaller isotopic dilution. Table 1 shows the data obtained from our tests. A larger amount of activity was recovered in the washings, as expected, when the 0.5 mm i.d. teflon transport tube was replaced with one of larger i.d. (0.8 mm i.d. PE/PP tube). In fact, the quest for higher specific activities urges many groups to switch from teflon to PE/PP as material of choice for the transport lines [4]. Unfortunately, this sort of material is not easily available world-wide in a small size so that a 0.8 mm i.d. was the smallest we were able to find. The variability observed in the results obtained with the first washing reflects the disparate conditions employed for the bombardment (15 μA, 5÷40 min) and the elapsed time between EOB and activity recovery (5÷60 min). In fact longer bombardments and, to a lesser extent, longer waiting times between the EOB and the next emptying operation, both contributed to increase the evaporation of target material and thus to decrease the volume of aqueous [^{18}F]fluoride actually leaving the target, with an obvious detrimental effect on the amount of activity reaching the hot-lab. Of course, both formation of little droplets on the walls of the tubing and break-up of the bolus during the initial delivery of the irradiated water, have a considerable importance too [5].

One more factor indirectly contributing to the percentage of activity recovered lay in the Dowex 1X8. In our opinion the resistance offered by the resin to the free passage of water was enough to slow down the flow so that, for the reasons above highlighted, less activity was left in the fine after target unloading. In fact, in a few cases, when the target water was transferred to the hot-cell directly, without passing through the resin, the recovered activity in

[1] A timer can be set on the program as an alternative. However, the remote-controlled fashion allows for a better optimization of the process in terms of time and it covers from possible delays in the transport.

the rinsing reached 6.8 %. Table 1 clearly shows that most of the residual activity in the fine was taken out with just one washing. Moreover, monitoring of the activity flow indicated that most of the activity was present in the first 1÷1.5 mL of rinsing water coming up. However, no serious attempts were carried out to optimize this volume. However, the potential of reducing the volume of deionized water used in the washing without much hampering the efficiency is particularly important should the extra-[^{18}F]fluoride be utilized for experimental and therefore needing to be dried.

Table 1: Percentage of recovered activity[1] in the first and second washing fraction[2]

	Recovered activitv (%)	
	0.5 mm i.d. (teflon)	0.8 mm i.d (PE/PP)
1st washing	1.37 ± 0.34	2.67 ± 0.45
2nd washing	0.34 ± 0.05	0.52 ± 0.06
Total (4.6mL)	1.71 ± 0.39	3.19 ± 0.51

[1]Values are calculated as mCi [^{18}F]F- (decay corrected at t_0) in the washing x 100 / mCi [^{18}F]F$^-$ come up after emptying the target (t_0). Data reported are the means and standard deviations for 4 experiments.
[2]An 8-second opening of V8 followed by 110 s of flushing with helium allowed to deliver to the hot-cell 2.3 mL of deionized water.

It must be pointed out that the reported results are related to our own facility (0.78 mL target material; 11-meter-long transfer fine from target to hot-cell, with a rise of 4.3 m). Obviously, smaller volumes and longer tubes can only enhance the advantages of the system [5]. Furthermore, in a few occasions during which the recovered activity was inexplicably low, the rinsing of the fine afforded a gain of even 30%, thus proving to be a powerful tool against troubles related to the dispensing of activity. Work is in progress to include also the target chamber in the washing procedure and to evaluate the possible extent of isotopic dilution of the recovered [^{18}O]H_2O.

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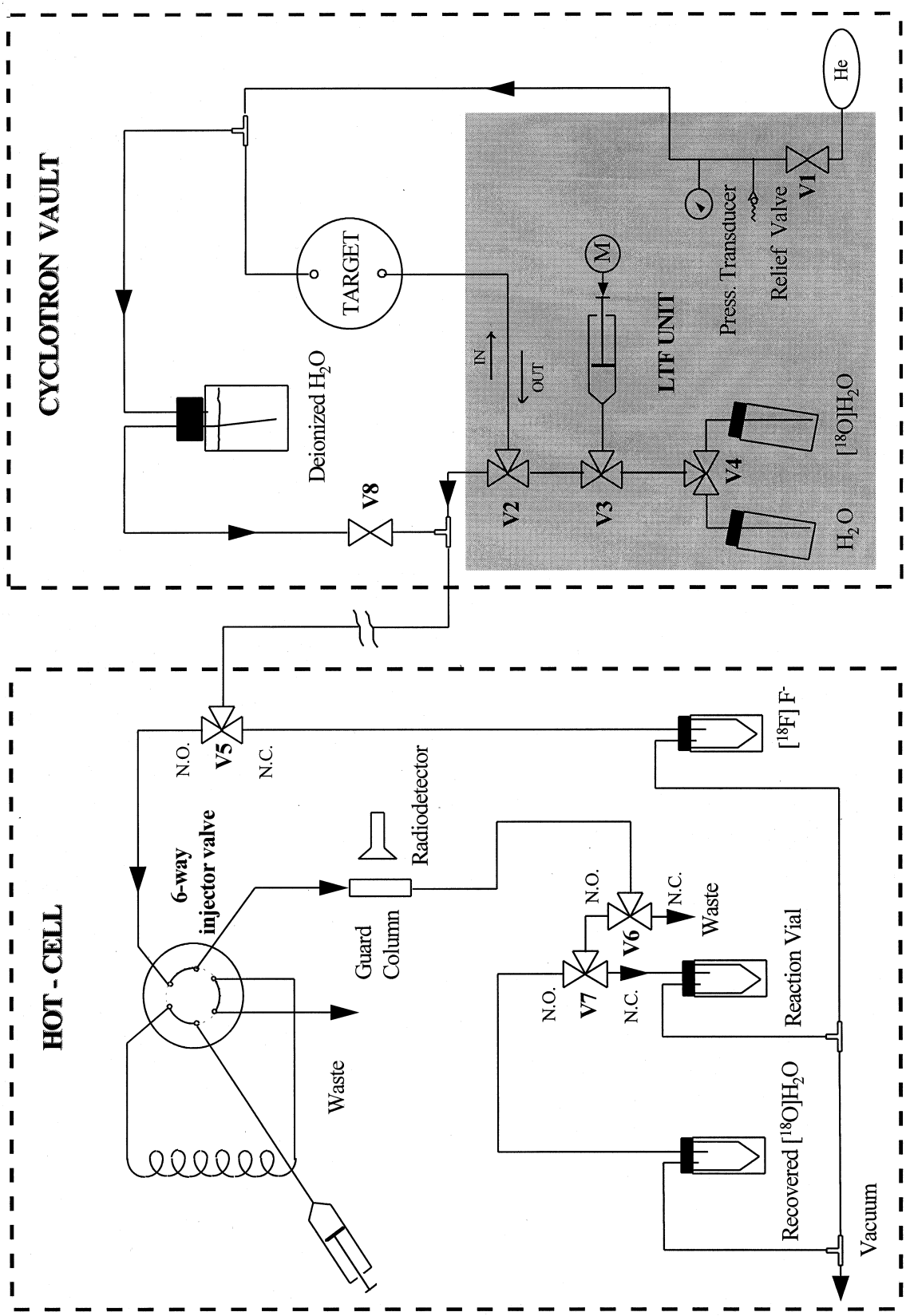

Fig. 1: Schematic drawing depicting LTF unit, [^{18}F]fluoride/[^{18}O]H_2O recovery apparatus and washing system setup