ADVANCED
CYCLOTRON SYSTEMS, INC.

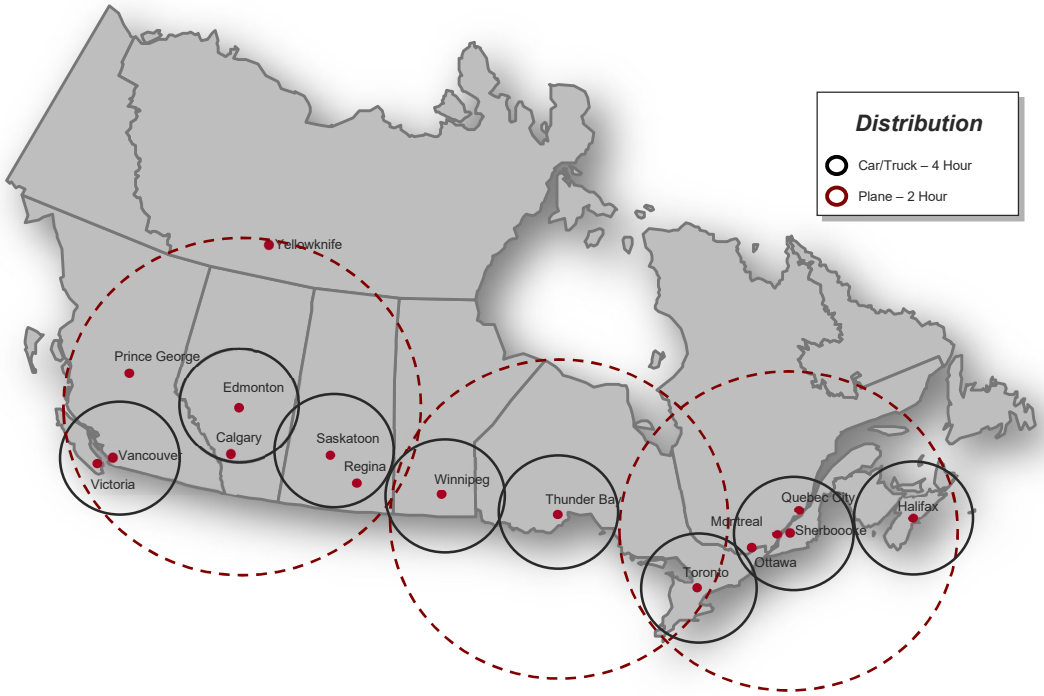
Cyclotron production of ^{99m}Tc (CYCLOTEC™) and ^{99}Mo (CYCLOMOLY™)

To date, more than 80% of all diagnostic nuclear medicine procedures in the world (~ 50 million per year) use technetium-99m (^{99m}Tc) based radiopharmaceuticals. Conventially,^{99m}Tc is obtained from molybdenum-99 (Mo-99) radioactive decay, which itself is produced in nuclear reactors. Frequent scheduled and emergency shutdowns of these reactors in recent years have led to repetitive Tc-99m supply crises and have forced governments and scientists to search for alternative sources of Tc-99m and other isotopes critical to the development of nuclear medicine.

Cyclotron production of CYCLOTEC™

The project was launched by ACSI in partnership with the University of Alberta (Edmonton) and the University of Sherbrooke in Quebec (city of Sherbrooke) in response to the NRCAN (Ministry of Natural Resources Canada) call for proposals on alternative methods of production of Tc-99m and/or Mo-99. ACSI has proposed to develop a commercial approach to production of T-99m and to build a national network of eight medium energy cyclotrons, which could meet the needs of all Canada not only for Tc-99m, but for other radionuclides used in clinical practice and research. This proposal was support by a ground breaking experimental work done at University of Sherbrooke where Tc-99m was produce using TR-19 cyclotron and successfully used for imaging in small animals [ref. 1]

Operational, planned, and potential centers and geographical areas



ADVANCED
CYCLOTRON SYSTEMS, INC.

In December 2010, NRCAN allocated a grant of 11 million dollars to ACSI as part of the NISP program (NON REACTOR-BASED ISOTOPE SUPPLY PROGRAM) to develop a pilot commercial production of Tc-99m using TR-24 cyclotrons. At the same time 8 million dollars were allocated to a TRIUMF led research group that was focusing on development of Tc-99m production using existing, lower energy TR-19 cyclotrons.

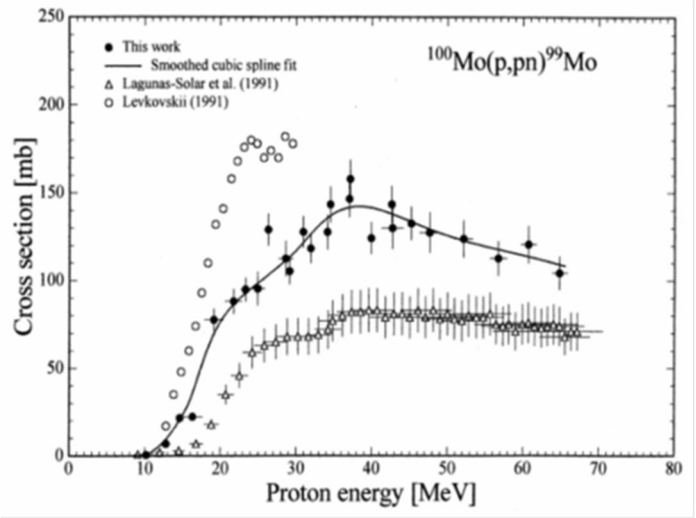
The NISP funded projects resulted the development of a full cycle of production and clinical testing of cyclotron produced Tc-99m (CYCLOTEC™) , and the establishment of two pilot systems based on TR-24 cyclotrons in Edmonton and Sherbrooke and TR-19 system in Vancouver operated by BC Cancer Agency in collaboration with TRIUMF.

In March of 2013, as part of a new program for the commercialization of alternative methods for the preparation of technetium-99m (ITAP-Isotope Technology Acceleration Program), additional $ 11 million were allocated Canadian research centers to continue development on the production of Tc-99m using cyclotrons.

The measured yields (~ 150 mCi/uA at saturation) for TR-24 suggest that a single six-hour irradiation at a current of 250 μA on the molybdenum target can yield about 18 Ci of CYCLOTEC™. Assuming 15% losses in the processing of the target and an average 10-hour interval between the end of irradiation and the injection to the patient (time spent on processing, packaging, shipping and waiting in the clinic), this activity is sufficient to supply a population of 3-5-million. A 300 μA TR-19 cyclotron can generate up to 10 Ci and 15 Ci of Tc-99m at the end 6 or 12 hour production cycle followed by separation of Tc-99m. TR-19 cyclotron installed at the BC Cancer Agency in Vancouver, can routinely produce 10 Ci of CYCLOTEC™ by bombarding a ^{100}Mo target with a current of 240 μA for 6 hours.

Cyclotron Production of CYCLOMOLY™

The use of a medium to high energy cyclotron has an additional advantage: Production of ^{99}Mo as a byproduct by the ^{100}Mo(p,xn) ^{99}Mo reaction. A 12-hour irradiation at 25 MeV with 500 μA current yields up to 3.4 Ci of cyclotron produced ^{99}Mo (CYCLOMOLY™), which can then be used as a generator of ^{99m}Tc directly in the radiopharmacy or can be shipped to another user. Since ^{99}Mo has a significant half-life, 2.75 days, CYCLOMOLY™ can be produced 1-2 times a week, performing longer irradiation when cyclotron is not used for production of short-lived radionuclides.



ADVANCED
CYCLOTRON SYSTEMS, INC.

CYCLOTEC™ and CYCLOMOLY™ Cyclotron Technology

ACSI manufactured cyclotrons are uniquely positioned for CYCLOTEC™ and CYCLOMOLY™ production. Unmatched reliability and high current make them ideal for regional commercial supply of Tc-99m and/or Mo-99. ACSI offers complete CYCLOTEC™ and CYCLOMOLY™ packages that include all necessary equipment, technology, and processes for production of Tc-99m and Mo-99. These packages include installation of ACSI manufactured cyclotrons, beam lines, targetry, target processing systems as well as complete technological cycle and training for production of CYCLOTEC™ and CYCLOMOLY™.

CYCLOTEC™ production on medium energy cyclotrons:

The ideal energy for ^{99m}Tc production is 22-23 MeV. At this energy the level of impurities produced during bombardment is still acceptable. The TR-24 cyclotron with up to 25 MeV variable energy and high current capabilities (300, 500 and 750 uA models) is ideally suited for this production. The high current solid target stations described below can be installed at the end of a beamline connected to the TR-24 cyclotron.

CYCLOTEC™ theoretical yields as a function of beam energy and current:

Energy [MeV]	Current [μA]	Theoretical Activity Tc-99m, 6 hours	
		GBq	Ci
16	60	77	2
18	150	227	6
	200	349	9
	300	524	14
23	300	822	22
	500	1370	37
30	300	N/A	N/A
	500	N/A	N/A

ADVANCED
CYCLOTRON SYSTEMS, INC.

CYCLOMOLY™ production on high energy cyclotrons:

Recently ACSI has developed and launched a new cyclotron model called the TR-FLEX. The TR-FLEX is based on proven TR-24 platform, but offers an extended energy range, up to 30 MeV. This cyclotron can be considered as a cost-effective alternative to large 30 MeV machine, such as Cyclone-30 and TR-30. Given that the physical dimensions of TR-24 and TR-FLEX cyclotrons are the same, the TR-24 facility design can be adapted to TR-FLEX cyclotron. Besides production of classical SPECT radioisotopes TR-FLEX can be used to generate sizable quantities of CYCLOMOLY™.

CYCLOMOLY™ theoretical yields as a function of beam energy and current:

Energy [MeV]	Current [μA]	Theoretical Activity Mo-99, GBq	
		12 hours	48 hours
16	60	---	---
18	150	4.2	14
	200	5.7	19
	300	8.5	28
24	300	77	257
	500	128	428
30	300	190	636
	500	317	1060

TR-24 and TR-Flex cyclotron installations configured
for CYCLOTEC™ and CYCLOMOLY™ production

ADVANCED
CYCLOTRON SYSTEMS, INC.

CYCLOTEC™ and CYCLOMOLY™ Target Technology

Both, CYCLOTEC™ and CYCLOMOLY™, isotopes are produced by irradiation of ^{100}Mo targets using proton beams generated by ACSI cyclotron.

CYCLOTEC™ can be produced by irradiation of small, coin-size, solid targets located directly on the cyclotron. The disadvantage of this irradiation is that no sizable quantatires of CYCLOMOLY™ can be produced using this type of targets, while the amounts of ^{99m}Tc are limited to approximately 3-4 Ci for 6 hours irradiation. When taking into account purification losses, as well as decay due to shipping and waiting for patient injection, the number of available doses become quite low. The cost of consumables per run, including the high cost of the ^{100}Mo make production of ^{99m}Tc in low quantities not economical, compared with the ^{99}Mo/^{99m}Tc generators.

Solid target holder for coins, capable of accepting 60 μA beam current

For high volume production of CYCLOTEC™ and CYCLOMOLY™ it is necessary to use a solid target station and high current ^{100}Mo solid target coupled with pneumatic target delivery system. The solid target station must be installed at the end of a beamline.

ACSI's solid target station for irradiation of targets at high current, 500 uA

^{100}Mo targets for ACSI target station