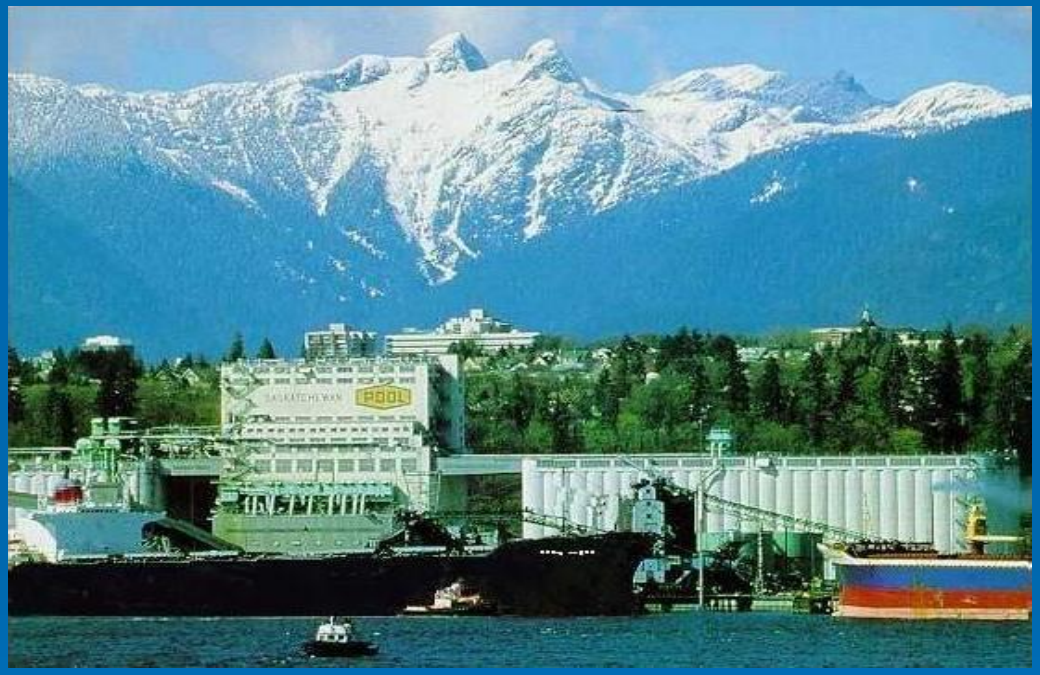
Multicentre Canadian Study to Measure the Safety and Efficacy of Radiosynoviorthesis (RSO)



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No financial Disclosures

CANADA IS A LARGE NORTHERN COUNTRY WITH MOST OF ITS POPULATION STRUNG WITHIN 100 MILES OF THE UNITED STATES BORDER

LONG HISTORY OF CANADIAN INVOLVEMENT WITH MEDICAL ISOTOPES SINCE CANADA PRODUCES MUCH OF THE WORLD'S URANIUM (AND UNTIL THIS YEAR MOST OF THE WORLDS MO-99)

Atomic Energy of Canada Limited

AECL

CANDU Owners Group Inc.

COG

"Excellence Through Collaboration"

nordion

SCIENCE ADVANCING HEALTH

ADVANCING NUCLEAR MEDICINE

ADVANCED CYCLOTRON SYSTEMS, Inc.

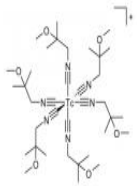
Gamma Technologies

Medical Isotopes

TRIUMF

Accelerator Targets

Isotope Production



Radiochemistry

cpdc Centre for Probe Development and Commercialization

Canadian Cent

Canadian Light Source

The Canadian Light Source is a

Prairie Isotope Prodi

Prairie Isotope Production Enterprise (PIPE)

UNIVE SASKAT

University of Saskatchewan (UofS)

Fedoruk Centre

SYLVIA FEDORUK CANADIAN CENTRE FOR NUCLEAR INNOVATION

SIMILARLY LONG HISTORY IN CANADA OF Radiosynoviorthesis (RSO)

- INITIALLY Y-90 COLLOID AVAILABLE THROUGHOUT CANADA AS ROUTINE PROCEDURE FROM 1983-2000
- SUPPLIED FROM MCMASTER UNIVERSITY NUCLEAR REACTOR IN HAMILTON, ONTARIO
- YEAR 2000 HAMILTON DECIDES TO STOP SUPPLY
- Y-90 AND RE-186 COLLOID AVAILABLE IN CANADA ONLY FROM CIS-BIO IN FRANCE AT HUGE INCREASE IN COST UNDER HEALTH CANADA *"SPECIAL ACCESS"* PROGRAM
- BUT MUST BATCH TREAT (3-4) PATIENTS TO BRING COST TO WITHIN PROVINCIAL GOVERNMENT REIMBURSEMENT RATES
- Y-90 AND RE-186 COLLOID WAS NOT EVER LICENCED FOR SALE BY ITS IMPORTER (ATOMED QUEBEC) IN CANADA

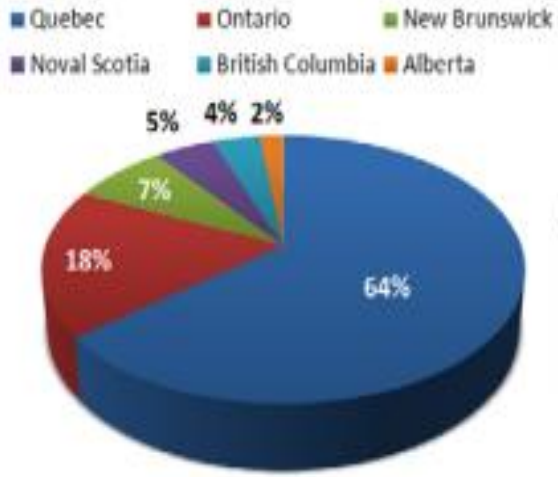
McMaster Nuclear Reactor

Reactor building in 2013.

CONTEMPORARY USE OF RSO

Statistics originate from the 2009 Canadian sales of Yttrium-90 (73,575 MBq). Accordingly, on an average of 185 MBq per knee, 398 knees injection were made in 2009. Worldwide, more than 22000 injections are made a year (4,168,537 MBq).

- Quebec: 64%
- Ontario: 18%
- New Brunswick: 7%
- Nova Scotia: 5%
- British Columbia: 4%
- Alberta: 2 %



For smaller articulations made with Rhenium-186, an average of 74 joints were injected in 2009, 100% was performed in Quebec. No injection was made with Erbium-169.

CANADIAN EXPERIENCE

2011 -- Health Canada Announces it Will No Longer Permit Y-90 or Re-186 Colloid Importation Into Canada Under "Special Access" Program

- *SAP is an exceptional mechanism to provide emergency access to drugs that are not available for sale in Canada.*
- *For the record, we have spoken with ATOMED, the Canadian distributor for Yttrium 90 and rhenium 186 manufactured by CIS-Bio and have asked what their plans have been for yttrium and rhenium in Canada. They responded by saying that they had no plans to seek market authorization in Canada. We have since explained that this is wholly unacceptable and that they need to regroup to put together a plan to seek market authorization in Canada.*

Sophie Hamel

Special Access Programme / Programme d'accès spécial Office of Risk Management / Bureau de gestion des risques Therapeutic Products Directorate / Direction des produits thérapeutiques

Health Canada / Santé Canada

Multicentre Canadian Study to Measure the Safety and Efficacy of Radiosynoviorthesis

- Health Canada agrees to allow importation of Y-90 and Re-186 colloid only under Clinical Trial Application (CTA) conducted through the University of Sherbrooke
- Trial enrolling 1,000 Y-90 and 500 Re-186 joints
- Current enrollment 159

Multicentre Canadian study to measure the safety and efficacy of synoviorthesis performed with Yttrium-90 or Rhenium-186 sulfide

PROTOCOL: CIMS-2011-03

Principal investigator: Éric Turcotte, MD

Co-investigators:

Joël Desroches, MD	François Raymond, MD	Jonathan Romsa, MD
Marcel Dumont, MD	Raymonde Chartrand, MD	Daniel Dionne, MD
Andrew Ross, MD	Francis Morin, MD	Jean-Pierre Mathieu, MD
Michel Picard, MD	Michel Leblanc, MD	John LeBlanc, MD
Carter Thorne, MD	Rachel Shupack, MD	Philip Cohen, MD
Douglas N. Abrams	Elaine Joughin, MD	Grégoire Blais, MD
Kennedy Mangera	Christine Molnar, MD	Bohdan Bybel, MD
Michel Leblanc, MD	Bevan Frizzell, MD	Dr. Nicole Leriche
Lucie Carrier, MD	Lucie Carrier, MD	

Multicentre Canadian Study to Measure the Safety and Efficacy of Radiosynoviorthesis cont.

The primary objective will be to assess the safety of an intra-articular administration of Yttrium-90 citrate colloid o Rhenium-186 sulfide. This will be done by evaluating:

- Side effects especially injection site reactions
- Blood cell count, liver and kidney function before and after RSO

The secondary objective will be to assess the efficacy on synovitis. This will be done by evaluating:

1. Joint pain proportion achieving a reduction of at least 20 on VAS 100mm scale
2. Patient's global assessment of disease activity proportion achieving a reduction of at least 20 on VA 100mm scale
3. Percentage of patients achieving an improvement Both 1 & 2
4. Functional disability as measured by HAQ
5. Duration of response (time to relapse of pain and/or increasing functional disability in the treated joints)
6. Physician's global assessment of disease activity

Multicentre Canadian Study to Measure the Safety and Efficacy of Radiosynoviorthesis cont.

Phase-III, prospective, open-label non-controlled trial.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA:

1. There is no age limit for RSO
2. Patient referred by a medical joint specialist (orthopedist, rheumatologist or internal medicine in the absence of local joint specialist)
3. Patient having a refractory inflammatory articular disease:
    a. Rheumatoid arthritis
    b. Spondyl-arthropathy:
        i. Psoriatic arthritis
        ii. Ankylosing spondylitis
        iii. Reactive arthritis
        iv. Enteropathic arthritis
    c. Other inflammatory joint disease:
        i. Behçet
        ii. Lyme disease
    d. Calcium pyrophosphate deposition arthritis
    e. Pigmented villo-nodular synovitis
    f. Hemophilic arthropathy
    g. Osteoarthritis
    h. Recurrent joint effusion after surgery or prosthesis
    i. Other undifferentiated arthritis
        i. Recurrent synovitis
        ii. Recurrent hydrarthrosis
        iii. Synovial thickening

Multicentre Canadian Study to Measure the Safety and Efficacy of Radiosynoviorthesis cont.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA:

4. Failure of medical therapy after 6 months
    a. Additionally, the patient has failed or had an incomplete response to at least 2 intra-articular long-acting glucocorticoid injections.
5. Clinical signs of an active mono or oligo synovitis
6. Joint X-ray, echo or MR showing minimal cartilage or bone destruction
7. Pain limits normal activities or requires significant analgesic medication

Multicentre Canadian Study to Measure the Safety and Efficacy of Radiosynoviorthesis cont.

CONTAINDICATIONS

1. Prior RSO within last 3 months in that joint
2. Collapse of the articular plateau or intra-articular fracture
3. Surgery or arthroscopy within last 6 weeks
4. Painful prosthesis
5. Joint infection, local skin infection, bacteremia
6. Joint puncture within last 2 weeks (increased risk of soft tissue necrosis along the needle track)
7. Pregnancy or breast feeding
8. Synovial cyst rupture
    a. If suspected, knee arthrography should be done at least 14 days before injection to localize the cyst and assess its communication with the articular cavity
9. Massive hemarthrosis
10. Generalized synovitis defined as more than 5 uncontrolled joints by clinical examination or 3 phases bone scan
11. Surgical synovectomy within 6months
    a. except arthroscopic synovial debulking
12. Cancer with bone metastases
13. Hypersensitivity, allergies or contraindication to the used radiopharmaceutical agent
14. Participation in any other ongoing clinical trial for the underlying inflammatory condition

Multicentre Canadian Study to Measure the Safety and Efficacy of Radiosynoviorthesis cont.

RADIOPHARMACEUTICALS

LARGE SIZE ARTICULATIONS (KNEE)

Yttrium-90 citrate is the preferred material for larger articulations such as the knee. See the table below for dose and volume.

Joint	Dose in MBq	Recommended volume (ml)
Knee	148 - 278	3.0

MEDIUM SIZE ARTICULATIONS (HIP, SHOULDER, ANKLE…)

Rhenium-186 sulfur colloid is the preferred agent for hip, shoulder, elbow, wrist, ankle and subtalar joints. Both the administered activity and the injected volume vary according to the volume of the joint to be treated. The total activity of Rhenium-186 in a single session should not exceed 370MBq.

Joint	Administered activity (MBq)	Recommended volume (ml)
Hip	111-185	3.0
Shoulder	74-111	3.0
Elbow	56-93	1.0-2.0
Wrist	37-74	1.0-1.5
Ankle	74	1.0-1.5
Subtalar	37-74	1.0-1.5

If requested and in certain circumstances, mid size articulations up to the size of the ankle can be performed with Yttrium following the approval by the direction board.

Joint	Dose in MBq, Yttrium	Recommended volume (ml)
Hip	185	3.0
Shoulder	93	3.0
Elbow	93	1.0-2.0
Ankle	74	1.0-1.5

Multicentre Canadian Study to Measure the Safety and Efficacy of Radiosynoviorthesis cont.

SAFETY – PRIMARY OUTCOME

The safety profile will be assessed by incidence of AEs. All the AEs will be described by system organ class and preferred terms and overall sorted by frequency. For the incidence of patients with agent-related AEs, a 95% Clopper-Pearson confidence interval will be provided.

EFFICACY – SECONDARY OUTCOME

Efficacy outcomes will be the clinical response at 3 months, 6 months and 1 year:

1. Joint pain- proportion achieving a reduction of at least 20 on VAS 100mm scale
2. Patient's global assessment of disease activity - proportion achieving a reduction of at least 20 on VAS 100mm scale
3. Percentage of patients achieving an improvement Both 1 & 2
4. Functional disability as measured by HAQ – proportion achieving a reduction of a least .2
5. Duration of response (time to relapse of pain and/or increasing functional disability in the treated joints)

    - Articular injection of steroids in the treated joint during follow-up is considered as a treatment failure, if it occurs more than 2weeks post RSO.
    - Acute radio induced synovitis within 2 weeks of RSO can be treated by intra-articular GC. This will not be a treatment failure.

The comparison will be done with a confidence interval approach based on a Chi^2-test for each of the above secondary criterion assessed at different times during the follow-up compared to the same criterion assessed at baseline.

CHUS
CENTRE HOSPITALIER UNIVERSITAIRE DE SHERBROOKE
Hôpital Fleurimont, 3001, 12e Avenue Nord, Fleurimont (Québec) J1H 5N4
Département de médecine nucléaire
Téléphone : (819) 346-1110

CIMS
Centre d'imagerie moléculaire de Sherbrooke

|

Site	Principal Investigator	**Subjects Treated**
CHUS, Sherbrooke, QC	Dr Éric Turcotte	**33**
CHUM, Montreal, QC	Dr Michel Picard	**87**
CH Pierre-Boucher Longueil, QC	Dr Lucie Carrier	**3**
CHR Rimouski-Neigette Rimouski, QC ***Closed***	*Dr Daniel Dionne*	*7*
CHR Trois-Rivières, Trois Rivières, QC	Dr Joël Desroches	**14**
Winnipeg Health Science Centre, Winnipeg,MB	Dr Bohdan Bybel	**9**
Vancouver Coastal Health,Vancouver, BC	Dr Philip Cohen	**13**
Southlake Regional Health Centre, Newmarket, ON	Dr Carter Thorne	**67**
CHUQ, Quebec City, QC	Dr Marcel Dumont	**20**
University of Calgary AHS, Calgary, AB	Dr Elaine Joughin	**8**
St-Joseph's Health Care London, ON ***Closed***	*Dr Johnatan Romsa*	*6*
CH Granby, Granby,QC	Dr Grégoire Blais	**3**
September 11th2012 – December 1st 2016		**TOTAL : 270***

*Yttrium and rhenium injections combined

Multicentre Canadian Study to Measure the Safety and Efficacy of Radiosynoviorthesis cont.

- Intention to add Sn -117m to RSO Protocol
- Possibly also Re-188 colloid (generator produced) for large joints.
- Protocol for Sn-117m is being worked out
- Comparison with Y-90 and Re-186 in treatment of rheumatoid arthritis
- Enrollment rates will be supported by:
  - Dedicated CRO assigned to oversee all sites
  - Continuous Sn-117m colloid ‘on demand’ (no need to batch patients)

QUESTIONS

1. The Canadian Clinical Trial using Re-186 and Y-90 is sponsored by which University?

a. University of Calgary
b. McGill University
c. University of Montreal
d. University of Sherbrooke

2. Which is the preferred radiotherapuetic agent for injection into shoulder joints?

a. Y-90 colloid

b. Tc-99m colloid

c. Re-186 colloid

d. Erbium-169 colloid

Which potential new radiocolloids may be used in the future in Canada?

a. Tin-177 colloid
b. Rhenium-188 colloid
c. Lu-177 colloid
d. Both a and b