Re-Inventing High-Dose-Rate Brachytherapy around Ytterbium-169

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July 17, 2019

The University of Iowa

Disclosure

Founder and president of pxAlpha, LLC, which is developing a rotating shield brachytherapy system

^{169}Yb Source Properties

- High specific activity, 93 keV avg photon energy, half-life of 32 days
- Similar radial dose function to ^{192}Ir
- Manufacturer: Source Production & Equipment Co., Inc (SPEC)
- FDA-Cleared
- Source dimensions: 0.60 mm diameter, 3.5 mm length, 1 mm^3
- Compatible with existing afterloaders, intracavitary or interstitial
- Maximum activity in 1 mm^3 volume: 27 Ci
  - Provides same dose rate in water at 1 cm as 10 Ci of ^{192}Ir

^{169}Yb Rationale Development

Ytterbium-169: Calculated physical properties of a new radiation source for brachytherapy

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Department of Medical Biophysics, University of Western Ontario and London Regional Cancer Centre, 790 Commissioners Road E., London, Ontario, Canada N6A 4L6

Med Phys 19, 696 – 703 (1992)

As a *temporary* implant source, two characteristics of ^{169}Yb are advantageous. First, it is possible to make very small ^{169}Yb sources of very high activity (~350 GBq/mm^3). Second, radiation protection is easier to achieve compared with higher energy sources such as ^{192}Ir and ^{137}Cs. This could reduce the bulk of shielding needed for afterloading equipment and treatment rooms, which may reduce the associated costs. However, because of the intermediate half-life, ^{169}Yb sources would need to be replaced more often than for sources having longer half-lives,

^{169}Yb Rationale Developing …

DOSIMETRIC CHARACTERISTICS, AIR-KERMA STRENGTH CALIBRATION AND VERIFICATION OF MONTE CARLO SIMULATION FOR A NEW YTTERBIUM-169 BRACHYTHERAPY SOURCE

Harold Perera, Ph.D., Jeffrey F. Williamson, Ph.D., Zuofeng Li, D.Sc., Vivek Mishra, Ph.D. and Ali S. Meigooni, Ph.D.

Radiation Oncology Center, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO 63110

Int J Radiat Oncol*Biol*Phys 28, 953 – 970 (1994)

and effective shielding of anatomical structures near the implant by placing 0.5–1.0 mm thick lead foils in the applicator system. In contrast, ^{192}Ir and ^{137}Cs require lead

^{169}Yb Rationale Developing …

Design of an Yb-169 source optimized for gold nanoparticle-aided radiation therapy

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Nuclear/Radiological Engineering and Medical Physics Programs, Woodruff School of Mechanical Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332-0405

Sunil Krishnan
Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030

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Department of Radiation Physics and Department of Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030

(Received 9 January 2014; revised 22 August 2014; accepted for publication 3 September 2014; published 30 September 2014)

Purpose: To find an optimum design of a new high-dose rate ytterbium (Yb)-169 brachytherapy source that would maximize the dose enhancement during gold nanoparticle-aided radiation therapy (GNRT), while meeting practical constraints for manufacturing a clinically relevant brachytherapy source.

Reynoso FJ, et al, Med Phys 41, 101709 (2014)

Patented ^{169}Yb Source

(12) **United States Patent**
Munro, III et al.

(10) **Patent No.:** **US 7,530,941 B2**
(45) **Date of Patent:** **May 12, 2009**

(54) **X-RAY AND GAMMA RAY EMITTING TEMPORARY HIGH DOSE RATE BRACHYTHERAPY SOURCE**

(75) Inventors: **John J. Munro, III**, North Andover, MA (US); **Matthew R. Hollows**, Westminster, MA (US)

(73) Assignee: **Best Medical International, Inc.**, Springfield, VA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 607 days.

(21) Appl. No.: **10/770,346**

(22) Filed: **Feb. 2, 2004**

(65) **Prior Publication Data**

US 2004/0254418 A1 Dec. 16, 2004

Related U.S. Application Data

3,351,049 A 11/1967 Lawrence

(Continued)

FOREIGN PATENT DOCUMENTS

EP 1 232 770 A1 8/2002

(Continued)

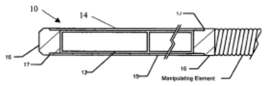
OTHER PUBLICATIONS

R K Das, V Mishra, H Perera, A S Meigooni and Jeffrey F Williamson: "A secondary air kerma strength standard for Yb-169 interstitial brachytherapy sources"; Phys. Med. Biol. vol. 40 (1995), pp. 741-756, XP-001205094; IOP Publishing Ltd.; Printed in the UK.

(Continued)

Primary Examiner—Samuel G Gilbert
(74) *Attorney, Agent, or Firm*—Muirhead & Saturnelli, LLC

(57) **ABSTRACT**



^{169}Yb Source Calibration Groundwork Laid

Air-kerma strength determination of a ^{169}Yb high dose rate brachytherapy source

J. J. VanDamme, W. S. Culberson,[a] L. A. DeWerd, and J. A. Micka
University of Wisconsin Medical Radiation Research Center, Madison, Wisconsin 53706

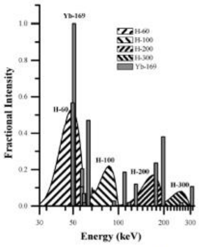
(Received 8 November 2007; revised 29 June 2008; accepted for publication 2 July 2008; published 7 August 2008)

The increased demand for high dose rate (HDR) brachytherapy as an alternative to external beam radiotherapy has led to the introduction of a HDR brachytherapy isotope ^{169}Yb. This source offers a dose rate similar to ^{192}Ir HDR sources, at about one fourth the effective photon energy. This work presents the calibration of this source in terms of air-kerma strength, based on an adaptation of the current, National Institute of Standards and Technology traceable, in air measurement technique currently used for ^{192}Ir HDR sources. Several additional measurement correction factors were required, including corrections for air scatter, air attenuation, and ion recombination. A new method is introduced for determining the ion chamber calibration coefficient $N_k^{^{169}Yb}$. An uncertainty analysis was also performed, indicating an overall measurement expanded uncertainty in the air-kerma strength (k=2) of 2.2%. © *2008 American Association of Physicists in Medicine.*
[DOI: 10.1118/1.2964094]

Key words: calibration, HDR

Med Phys 35, 3935-3942 (2008)

^{169}Yb Source Calibration Groundwork Laid



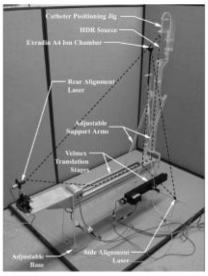
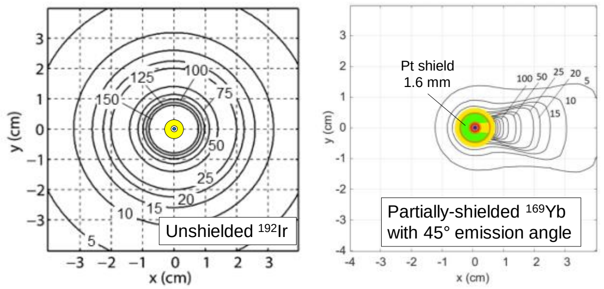


FIG. 3. The seven-distance measurement apparatus.

VanDamme et al, Med Phys 35, 3935-3942 (2008)

^{169}Yb Sources can be Effectively Shielded



From Quentin Adams and Karolyn Hopfensperger

What can be done with a partially-shielded HDR source?

Institute of Physics Publishing — Physics in Medicine and Biology
Phys. Med. Biol. 47 (2002) 2495–2509 — PII: S0031-9155(02)35423-X

Possibilities for intensity-modulated brachytherapy: technical limitations on the use of non-isotropic sources

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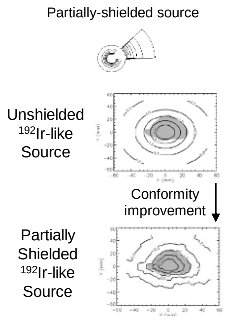
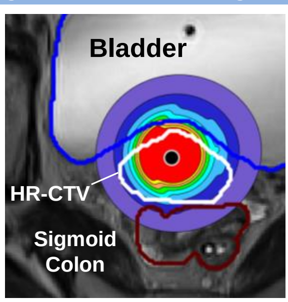
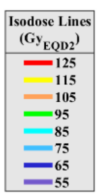
Received 4 April 2002, in final form 20 May 2002
Published 4 July 2002
Online at stacks.iop.org/PMB/47/2495



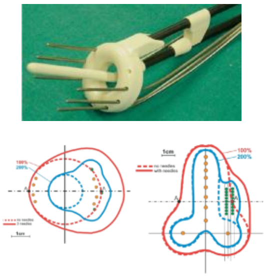
Challenges with Cervical Cancer High-Dose-Rate Brachytherapy

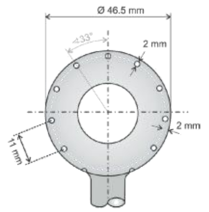




Includes external beam radiotherapy dose: 1.8 Gy x 25

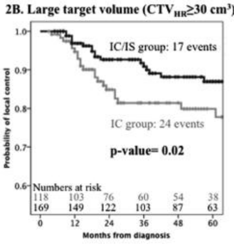
Interstitial HDR-BT Improves Dose Distributions





Images from Kirisits et al, IJROBP 65, 624-30 (2006)

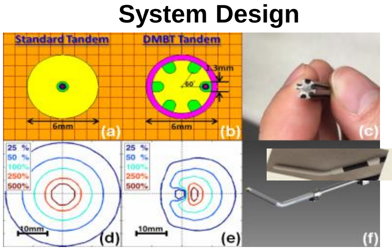
The Intracavitary/Interstitial Approach Works



- RetroEMBRACE: Retrospective study completed prior to EMBRACE I (2008)
- Local control at 3 years for HR-CTVs ≥30 cm^3
  - 92% at centers practicing IC/IS (n=169)
  - 82% at centers practicing IC only (n=118)
- EMBRACE II: Launched in 2016
  - ≥20% of patients at a participating center must receive IC/IS

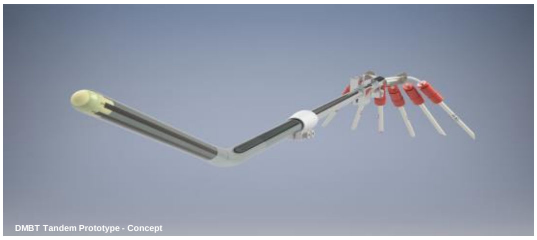
L. Fokdal et al, Radiother Oncol **120**, 434-440 (2016)
Pötter et al, "The EMBRACE II study..." Clin Transl Radiat Oncol **9**, 48-60 (2018)

Dynamic Modulated Brachytherapy (DMBT) System Design



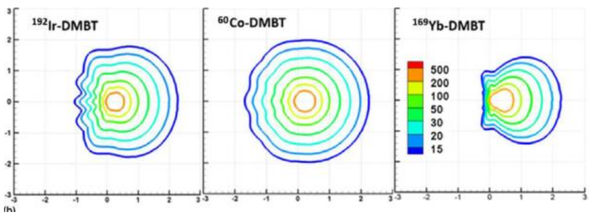
From William Song, Ph.D. Han *et al*., Int J Radiat Oncol Biol Phys 2016;96(2):440-448.

DMBT Design



From William Song, Ph.D.

DMBT with ^{169}Yb



Axial dose distributions

From Safigholi et al, Med Phys 44, 6538-6547 (2018)

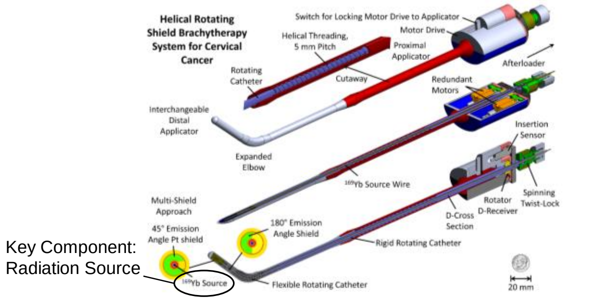
DMBT in Cervical Cancer Works Better with ^{169}Yb than with ^{192}Ir

For 45 patients with HR-CTV doses normalized to the same D_{90} delivered with ^{192}Ir using conventional tandem-and-ring:

- Mean bladder D_{2cc} reduced by:
  - 4.07% for ^{192}Ir-based DMBT
  - 5.13%, for ^{169}Ir-based DMBT
- Mean rectum D_{2cc} reduced by:
  - 3.17% for ^{192}Ir-based DMBT
  - 4.65% for ^{169}Yb-based DMBT
- Mean sigmoid D_{2cc} reduced by:
  - 3.63% for ^{192}Ir-based DMBT
  - 4.34% for ^{169}Yb-based DMBT

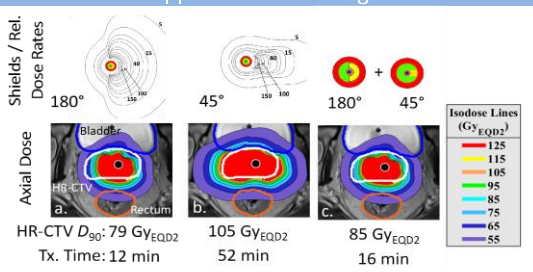
Safigholi et al, Med Phys 44, 6538-6547 (2018)

Rotating Shield Brachytherapy for Cervical Cancer



From Bounnak Thammavong

The Multi-Shield Approach to Reducing Treatment Times



For the full story and results, please attend Hopfensperger et al, TH-A-301-4, 7:30 am Session

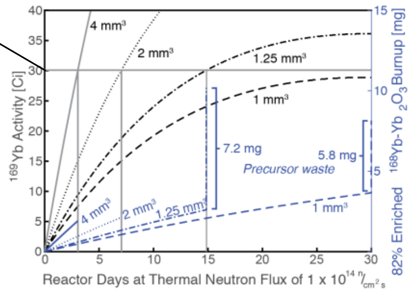
Non-invasive cervical cancer HDR sounds great. What's the catch?

- ^{169}Yb is expensive to generate
- We estimate \$55,000 / yr in 82%-enriched ^{168}Yb-Yb_2O_3 is needed to generate 1 clinic-year of ^{169}Yb in a 1 mm^3 source
- This would be pure overhead beyond the cost to generate ^{192}Ir, which has a very inexpensive precursor that is essentially \$0
- Making ^{169}Yb economically viable requires a strategy for cost-effective ^{169}Yb production

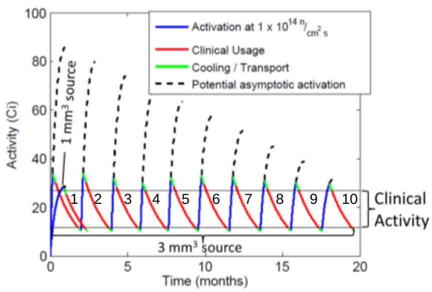
How to not waste expensive precursor and reactor time

Goal activity for shipment: 30 Ci

Conventional-sized sources (~1 mm³) are inefficient to activate and have high precursor waste



^{169}Yb Activation / Re-activation Approach



Summary:

For a 1 mm³ ^{169}Yb source:
- One activation possible
- ~6 mg of ^{168}Yb precursor discarded per activation.
- Precursor cost is $692/mg

For a 3 mm³ ^{169}Yb source:
- 10 Activations possible
- ~6 mg of precursor discarded *after 10 activations*
- Source is 0.6 – 0.69 mm in diameter, 8 – 10.5 mm long

Flynn RT et al, *Med Phys 46,* 2935-2943 (2019)

^{169}Yb Source Generation Conclusions

- The key to cost-effective ^{169}Yb source production is re-activation, which requires increasing source volume
  - Going from conventional 1 mm³ to 3 mm³ results in 75% cost savings
  - Estimated precursor cost per clinic year drops from $55,000 to $14,000
- Longer sources limit allowable curvature in applicators
  - This is a solvable RSBT applicator design challenge
  - The unviable economics of forcing ^{169}Yb into the ~1 mm³ source volumes used for ^{192}Ir is a harder challenge to address

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Prostate Cancer Statistics

- Much larger market potential than cervical cancer
- 175,500 new diagnoses expected in 2019
- 11% of men expected to be diagnosed with prostate cancer at some point during their lifetime (SEER 2019)
- 5-year relative survival rates for localized prostate cancer are >99%
- 32,000 deaths expected in 2019, 2nd highest for cancer death in men

Siegel et al, "Cancer Statistics, 2019," CA Cancer J Clin 69,7-34 (2019)

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One-Shot Prostate HDR-BT Clinical Results Summary

Series (Last update)	Dose	# Patients	Disease Risk	Years after for control estimate	Biochemical Control	Grade ≥ 3 Toxicity (%)			
						Acute		Late	
						GU	GI	GU	GI
Mt. Vernon Hospital, UK (2017)	19 Gy x 1 20 Gy x 1	24 26	Int, High Int, High	4.0 y	94%	≤9	0	2	0
Santander, Spain (2018)	19 Gy x 1 20.5 Gy x 1	60 60	Low, Int Low, Int	6.0 y 6.0 y	66% 82%	0 0	0 0	0 0	0 0
Toronto Sunnybrook (2017)	19 Gy x 1	87	Low, Int	2.25 y	92%	1.1	0	1.1	0
Oakland U., Michigan (2019)	19 Gy x 1	68	Low, Int	5 y	73.4%	0	0	0	1%

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Three of Four Groups are Suggesting Dose Escalation

"A strategy of focused ***dose escalation*** may be more relevant in prostate cancer patients treated with a single dose of HDR-BT as the pattern of relapse after 19 Gy occurs in areas previously encompassed by the disease, and insufficient biochemical control with this dose fractionation has been reported also by other authors (Prada et al (2016))."
- Mendez, …, Morton, Brachytherapy 17, 291-297 (2018)

"Biochemical control data (for 20.5 Gy x 1) will require more mature data. In the future, if these data compared with LDR brachytherapy were worse, it would be ***necessary to escalate doses*** to the entire prostate or use focal boost to a higher dose."
- Prada et al, Brachytherapy 17, 845-851 (2018)

"Future studies of single-fraction HDR monotherapy should focus on partial or whole gland ***dose escalation (above 19 Gy x 1)***."
- Siddiqui ZA, …., Krauss DJ, Int J Radiat*Oncol*Biol*Phys, Accepted for publication Feb. 2, 2019

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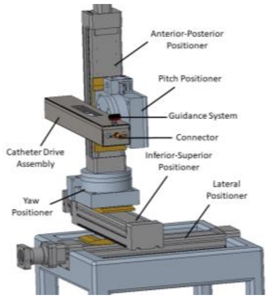
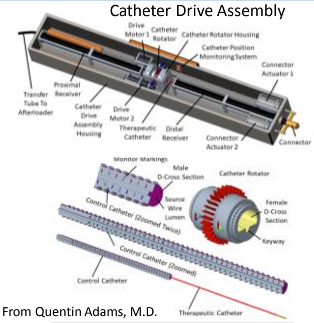
Next-Generation Brachytherapy For Prostate Cancer

Robotic *RSBT* Delivery System

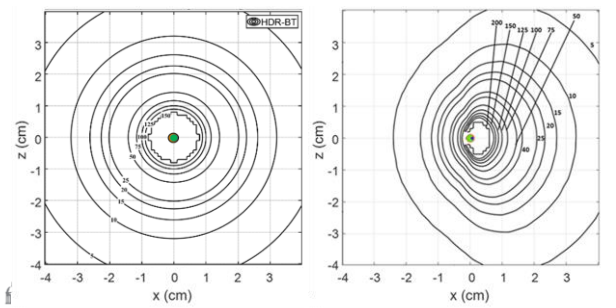


Catheter Drive Assembly



From Quentin Adams, M.D.

Unshielded vs. Shielded ^{169}Yb Interstitial Source



Prostate RSBT Dosimetric Results

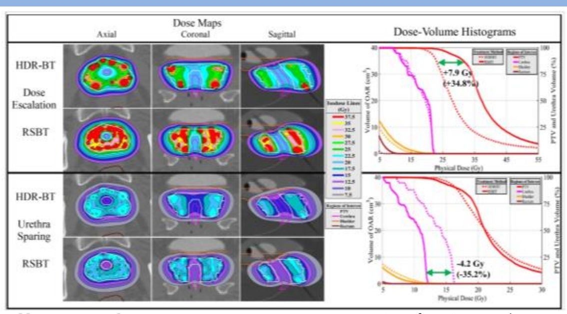
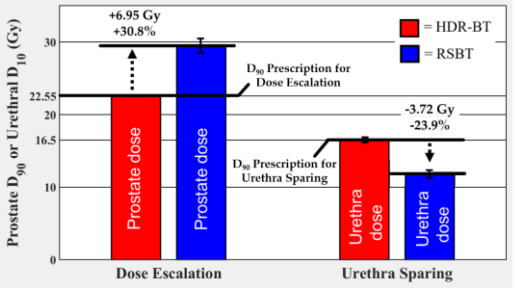


Figure from Quentin Adams, M.D.

Dosimetric Results for 26 Patients



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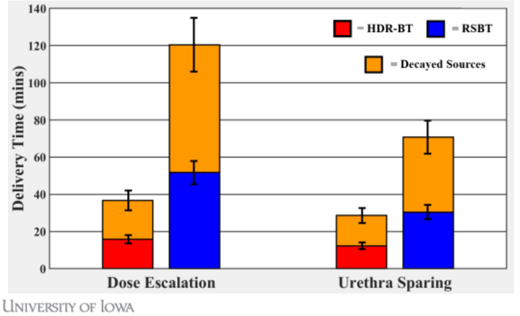
Treatment times: 26 Patients



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Prostate Cancer RSBT Conclusions

- Major dosimetric advantage relative to conventional HDR-BT
  - 30.8% boosting on average (n = 26) for dose escalation
  - 23.9% urethral sparing on average (n = 26) for boost therapy
- Simple delivery approach that meets our key specifications:
  - Needles remain flexible, multiple needle insertion depths possible
  - One shield is inserted in the needles at a time – no inter-needle interference
  - Delivery times reasonable with fresh sources:
    - Around 50 minutes for monotherapy and 30 minutes for boost therapy with a 27 Ci ^{169}Yb source

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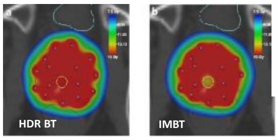
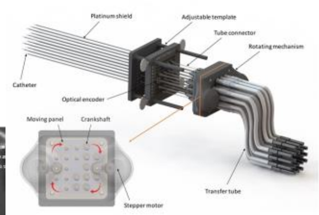
Prostate IMBT System Design from McGill (Enger) Group

- **AIM-Brachy** system
  - Recently developed prototype for dynamic interstitial IMBT
  - Potential application: prostate cancer
  - Collimation of ^{169}Yb source using platinum shields





From Shirin Enger (2019)

For updated information, attend: Famulari et al, TH-A-301-11, 7:30 am session

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The University of Iowa

Faculty
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- Karolyn Hopfensperger, B.S. (BME)
- Jirong Yi, B.S. (ECE)

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- Bounnak Thammavong, M.A.

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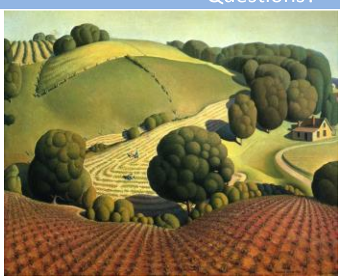
- Wes Culberson (UW-Madison)

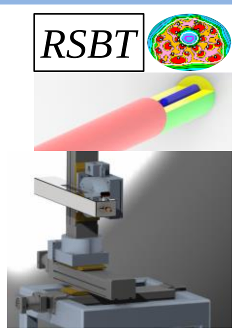
NIH National Institute of Biomedical Imaging and Bioengineering
R01 EB020665

NIH National Cancer Institute
R41 CA210737 (STTR Phase I)

Questions?



Young Corn,
by (Iowan) Grant Wood (1931)



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