PROSPECTS FOR PROGRESS IN THE DEVELOPMENT OF RADIOPHARMACEUTICAL THERAPIES

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April 13, 2014

Conflicts of interest

- None

Objectives

- Review sentinel historical events in the evolution of therapeutic radiopharmaceuticals
- Review a recent prospect for an advance in practice practice
- Are there prospects for future novel applications

The underlying principles of R-P therapy

- Treatment success with minimal toxicity is predicated on a favorable differential concentration of the R-P in diseased tissue volume
- Death of the diseased cells will achieve relief or a cure.
  - This is the ideal model for cancer therapy
- Reduction of diseased tissue bulk will moderate symptoms/disease progression
  - eg; Treatments of metastatic bone disease or NETs
- Death of effector cells will moderate the disease process
  - eg: ^{131}I therapy of Graves' disease, nodular goitres or synovia

Journal of the American Medical Association

May 11, 1946, Vol 131, No. 2

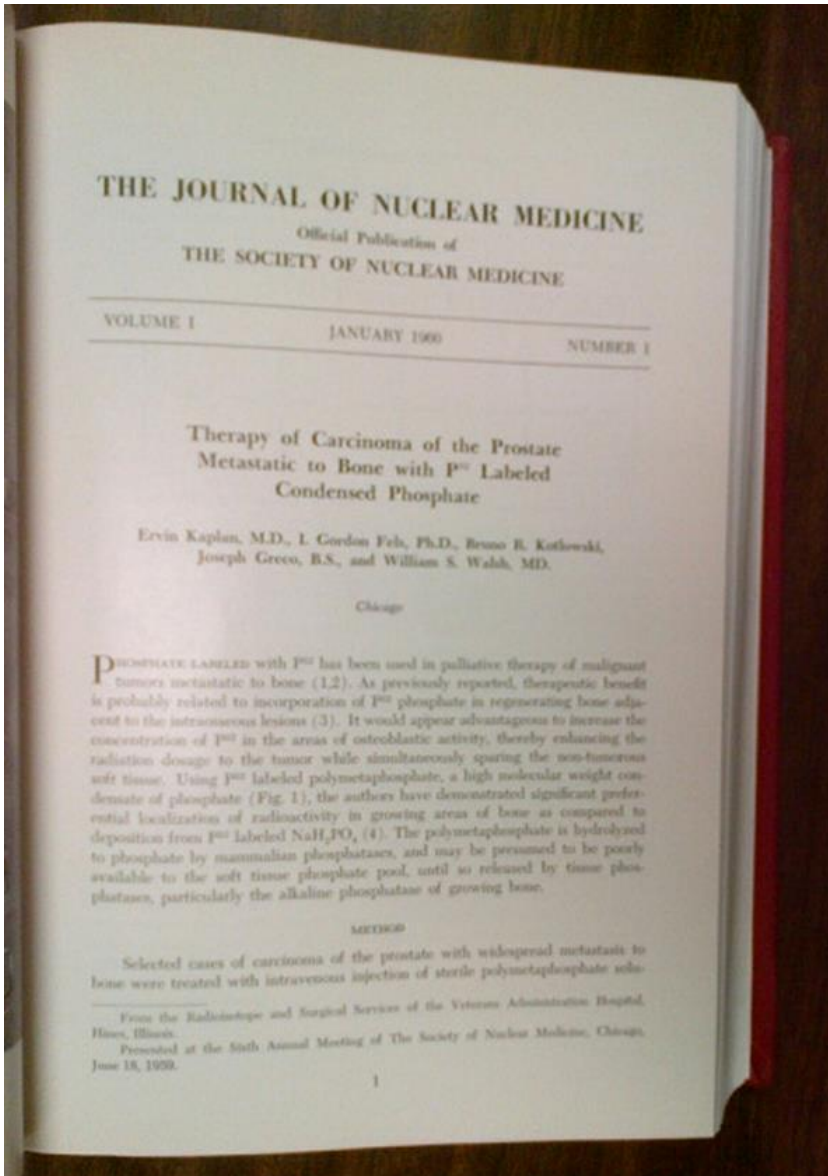
- RADIOACTIVE IODINE IN THE STUDY OF THYROID PHYSIOLOGY: VII. The Use of Radioactive Iodine Therapy in Hyperthyroidism 81-86
- SAUL HERTZ, M.D.; ARTHUR ROBERTS, Ph.D.
- THE TREATMENT OF HYPERTHYROIDISM WITH RADIOACTIVE IODINE 86-91
- EARLE M. CHAPMAN, M.D.; ROBLEY D. EVANS, Ph.D.

A Look over our Shoulders

Therapy of Carcinoma of the Prostate Metastatic to Bone with 32P-Labelled Condensed Phosphate.

Ervin Kaplan MD, I Gordon Fels PhD, Bruce R Kotlowski, Joseph Green BS and William S Walsh MD.

J Nucl Med 1;1:1960



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VOLUME 1 JANUARY 1960 NUMBER 1

Therapy of Carcinoma of the Prostate Metastatic to Bone with P^{32} Labeled Condensed Phosphate

Ervin Kaplan, M.D., I. Gordon Fels, Ph.D., Bruno R. Kotlowski, Joseph Green, B.S., and William S. Walsh, M.D.

Chicago

PHOSPHATE LABELED with P^{32} has been used in palliative therapy of malignant tumors metastatic to bone (1,2). As previously reported, therapeutic benefit is probably related to incorporation of P^{32} phosphate in regenerating bone adjacent to the intraosseous lesions (3). It would appear advantageous to increase the concentration of P^{32} in the areas of osteoblastic activity, thereby enhancing the radiation dosage to the tumor while simultaneously sparing the non-tumorous soft tissue. Using P^{32} labeled polymetaphosphate, a high molecular weight condensate of phosphate (Fig. 1), the authors have demonstrated significant preferential localization of radioactivity in growing areas of bone as compared to deposition from P^{32} labeled NaH_2PO_4 (4). The polymetaphosphate is hydrolyzed to phosphate by mammalian phosphatases, and may be presumed to be poorly available to the soft tissue phosphate pool, until so released by tissue phosphatases, particularly the alkaline phosphatase of growing bone.

METHOD

Selected cases of carcinoma of the prostate with widespread metastasis to bone were treated with intravenous injection of sterile polymetaphosphate solu-

From the Radioisotope and Surgical Services of the Veterans Administration Hospital, Hines, Illinois.

Presented at the Sixth Annual Meeting of The Society of Nuclear Medicine, Chicago, June 18, 1959.

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Characteristics of suitable isotopes and R-P

- Appropriate half life
- Appropriate energetic emissions (beta, alpha) with a high likelihood of killing the target cells
- High binding affinities to target cells
- Rapid excretion of non-targeted R-P
- Adequate clinical response
- Availability and price

The historical progression of bone met therapy

- ^{32}P Phosphate (1960s)
  - Simple chemistry
  - Toxicity significant
  - No life extension
  - Pain relief for up to a year but average only 6 weeks (Cheung and Driedger, 1980)
- ^{89}SrCl and ^{153}SmEDTMP (1980s)
  - Less toxicity; radoionuclide/chemo combination therapies possible
  - No life extension but reduced morbidity and cost of care for longer times
- $^{223}RaCl_2$ (2013)
  - Low toxicity
  - Average 3 month life extension for treated prostate cancer pts

Modelling of the transition from tumour embolus to bone metastasis

- Stephen Breen's PhD thesis circa 1988
- Calculation of tumour dose from ^{89}Sr as a function of size of the met
- Smaller mets receive a larger radiation dose
- Raised question whether a better use of radioisotope therapy would be as adjuvant administered early to high-risk patients
- Problem:
  - Need to recruit large populations in a very costly clinical trial

Comparing alpha and beta emitters

- Alpha particles have only 1/10-1/100 the range of beta rays
  - Implications;
    - Larger dose to target cells
    - Radiation events occurring in the extra-cellular environment are largely biologically irrelevant
- Alpha LET is ~1000X greater than beta decays
  - Implication; alphas kill with few hits (~1-5) compared to betas (hundreds)

Xofigo for endocrine-resistant prostate cancer

- $^{223}RaCl_2$
- Trials demonstrated improved survival (11.3 vs 14.9mos) in patients with otherwise intractable bone pain
- This is the first time that therapy of bone pain palliation has provided a survival benefit
- Would Xofigo be even more effective if used earlier in the disease progression a la Breen's modelling for strontium?
  - Could we do a practical clinical trial to assess conditions that maximize life extension?

And now for something completely different

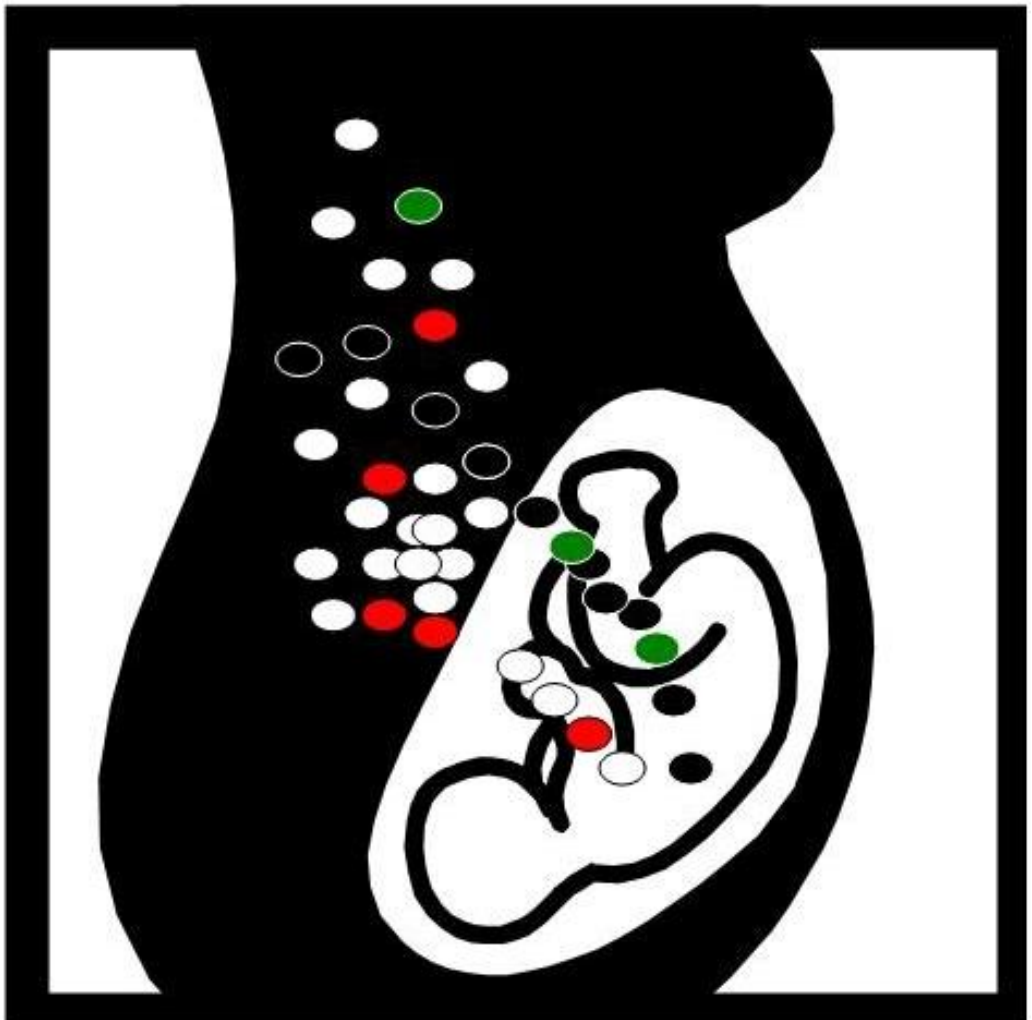
Albert Einstein

“If at first the idea is not absurd, then there is no hope for it.”

The chimera

Int J Mol Epidemiol Genet1(4); 2010

Introduction to microchimerism:



Micro-chimerism seems to play a critical role in the etiology of auto-immune diseases:

- Scleroderma
- Graves' disease
- Rheumatoid arthritis
- Type I diabetes mellitus
- Biliary atresia
- The diagnostic criterion has been the presence of lymphocytes with y chromosomes in biopsies of female tissues where there is a history of male conception(s) or of Barr bodies in males with these diseases.
- DNA sequencing will likely reveal female-female micro-chimerism as well

Target patient selection

- The remainder of this discussion will be focused on women with auto-immune states and in whom male T cells have been demonstrated.

Radionuclide therapeutic opportunity?

- A therapeutic agent that targets cells with y chromosomes could be curative for women with acceptable toxicity and without necessarily incurring loss of normal organ function
- A single radiotherapeutic agent would have utility for the entire range of auto-immune diseases attributable to mother-son micro-chimerism

Radiosynoviectomy

- What is the primary target for radio-synoviectomy in patients with rheumatoid arthritis?
  - Hypertrophied synovium?
  - Chimeric T-cells?

Microchimerism in rheumatoid nodules of RA patients

William FN. Chan, Christopher J. Atkins, David Naysmith, Nicholas van der Westhuizen, Janet Woo and J. Lee Nelson. Arthritis Rheum. 2012 February; 64(2): 380–388.

- Rheumatoid Nodules from 21% of female patients contained male DNA (range: <0.5–10.3 gEq/105).
- A fetal or maternal source was identified in all patients who tested positive by HLA-specific qPCR.

Are there cell surface markers for the Y chromosome?

- PATENT: Antigenic surface structure of bovine sperm associated with the y chromosome US 20090305270 A1
- ABSTRACT: The present invention relates to an antigenic surface structure of sperm cells associated with the Y chromosome, to the molecules, in particular antibodies, directed against this antigenic structure and to a method for characterizing cells carrying only the Y chromosome through the interaction between this antigenic structure and the molecules directed against said structure.
- CHALLENGE: Is a comparable surface marker present on chimeric male T cells of women with auto-immune disease?
- EXPERIMENTAL POSSIBILITY: Can chimeric T cells be stained with marked antibody?

Theoretical considerations

- A monoclonal radio-labelled antibody directed against surface proteins and that could be systemically administered might be possible
- Can a cytocidal radiation dose be administered to T cells?
  - Lymphocytes among the most radio-sensitive populations: a single acute dose of 500 mSv is lethal
- Will systemic delivery to treat circulating as well as peri-articular T cells be more effective than intra-articular application in control of non-articular rheumatoid arthritis symptoms?
- Might the same therapeutic agent prove therapeutic across the spectrum of auto-immune diseases?

Conclusion

- This is an interesting time to be active in investigative nuclear medicine
- The on-going evolution of molecular and personalized medicine concepts challenge us to rethink even our most deeply embedded understanding of our tools.
- Development of ever-improving therapeutics is more a cyclic than a linear process and it requires us to periodically re-evaluate our assumptions and re-plot our course.