Cinderella

Public Health Matters in 1906

In 1906 GB Shaw wrote *The Doctors Dilemma,* a play about ethical problems encountered by six doctors, all male, trying to cure patients with advanced tuberculosis. Shaw wrote his, as usual, long preface to this play that he summarized in 14 statements.

Table 1

Statements from Preface to The Doctors Dilemma
1. Nothing is more dangerous than a poor doctor, not even a poor employer or a poor landlord. (…) 12. Do not try to live forever. You will not succeed. (…) 14. Take the utmost care to get well born and brought up. This means that your mother must have a good doctor. Be careful to go to a school where there is what they call a school clinic, where your nutrition and teeth and eyesight and other matters of importance to you will be well attended to. Be particularly careful to have all this done at the expense of the nation, as otherwise it will not be done at all, the chances being about forty to one against you being able to pay for it directly yourself, even if you know how to set about it. Otherwise you will be what most people are at present: an unsound citizen of an unsound nation, without sense enough to be ashamed or unhappy about it.

What else is new?

Everybody needs a good mother, a good doctor and a government willing to keep health care costs affordable.
The average lifespan of citizens in the Western World increases gradually in the middle of the 19th century from 40 to 78 years of age due to the actions of 'Public Health' officials, employed by the State, securing cleaner air, better sewer systems, safer drinking water, better nutrition, childhood vaccinations, etcetera.
If physician/investigators find a cure for all forms of cancer tomorrow it would only increase the average lifespan of citizens in the Western world by 6-12 months, and be totally insignificant for citizens in less 'developed' countries, who would continue to die early from problems caused by poor preventive public health care and other infra structure problems.

Table 2

Ehrlich's 4Gs plus 1

Number	G in German	G in English	E.'s Solution
1	Geld	Money	Emperor Wilhelm II
2	Gluck	Luck	Animal models of human diseases
3	Geduld	Patience	E. had this in abundance
4	Geschick	Talent	See above
5	Gewin	Profit	No, Others profited from E's IP

Paul Ehrlich, Nobel Prize winner in Medicine in 1908 recommended future physicians/investigators interested in emulating him to search for

'Magic Bullets'

Magic, because bullets *(drugs)* would heal diseased tissues of the patient while sparing his healthy tissues. In a modern phrase: *Targeted Therapy.* Ehrlich claims his successes were due to the first four Gs in Table 2. He never was interested in making a profit, number 5 Gewin.

Fast Forward to 2011

By 2011 the R&D of a new drug/therapy has become more complicated than in 1908. Doctors are no longer leaders, like Ehrlich, in medicinal drug development. They have delegated their financial and managerial matters to others: such as CEOs of global pharmaceutical firms or health insurance companies and financial officers of hospitals. Such individuals live by a their new version of the golden rule:

'The guy with the gold makes all the rules.'

In contrast taxpayers/patients still consider physicians the right people to decide what is good or bad for them and often willingly follow the advice of their doctors. One of the reasons for this lingering public trust is that doctors have an international ethical code of behavior, the Physicians Charter, derived from the original oath of Hippocrates, which includes:

> *"Do no harm* (to your patient) *and make sure you do not have direct or indirect financial conflicts in the delivery of your patient care.* "

By 2011 two new dilemmas have joined the 5Gs of table 2:

1. Are Physician/Investigators still willing to initiate their own clinical research or do they prefer to follow blindly the rules of the guy with the gold?
2. Are Physician/Investigators able to deal with the ever-growing body of hard to understand and interpret Rules and Regulations that clinical investigators need to adhere to (at great emotional and financial costs)?

December 2009: Cinderella ready to dance

The Pharmaceutical Industry abandons the R&D of drugs with insufficient revenue generating potential. In December 2009 Van Bekkum and Vriesendorp established Cinderella Therapeutics Foundation to complete the R&D of promising but abandoned drugs. Cinderella's strategy contains four novel concepts:

1. Selecting new drugs to be developed exclusively on the basis of an anticipated high therapeutic ratio
2. Abandoning the profit motive as the driving force of an enterprise. The only goal is to secure better therapies for diseases, which currently cannot be treated adequately. No patents, no registration, no marketing costs. R&D costs decrease dramatically.
3. Open source principle; All projects are described in detail and updated regularly on Cinderella's website.
4. The great majority of current Cinderella projects, not all dealing with cancer, utilize a phase 2 approach: Single arm studies in less than 50 patients, which can be completed in 3 years.

The First Cinderella Project

Radiolabeled Immunoglobulin Therapy (RIT) has a high therapeutic ratio in patients with *'liquid'* tumors, leukemia's or lymphomas, which constitute only 5% of all cancers. The remaining 95% of cancer patients have a *'solid'* tumor arising in a solid organ, such as kidney, colon, brain, pancreas, etc. IV administered radiolabeled IgG, does not target solid tumors hiding behind a high Blood Tumor Barrier (BTB). The BTB can be bypassed by direct intra-tumoral (IT) injection of a radioimmunoconjugate (RIC). IgG has only 2 Antigen Binding Sites (ABS). After IT administration 50% of IgG will return to the circulatory system in 48 hours. IgM has 10 ABS and more than 90% of the IT administered radioactivity is retained in the tumor.

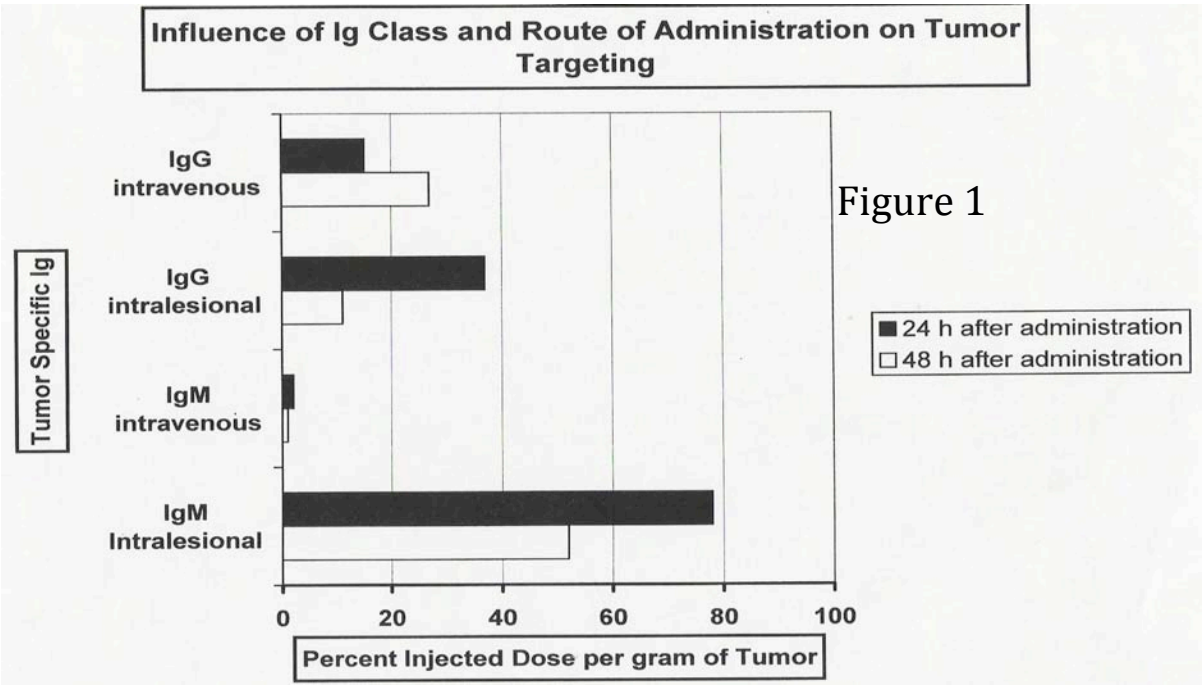


Figure 1

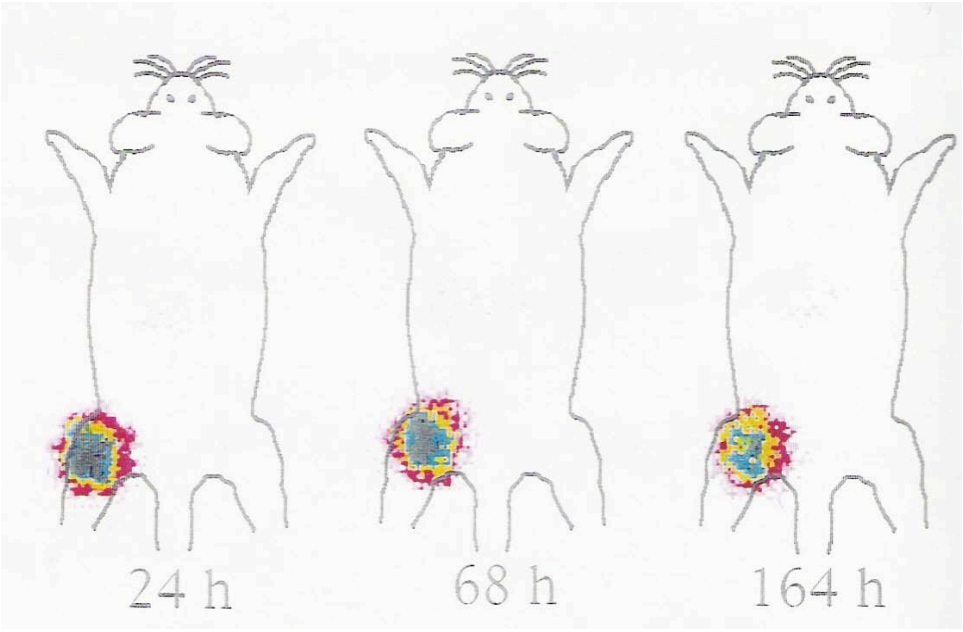


Figure 2. Sequential gamma camera scans of nude mouse carrying a human H&N tumor xenograft. Hours after IT administration of In-111 labeled tumor reactive IgM are noted.

Most solid tumors have a tumor matrix containing Tenascin-C (TNC), an extracellular matrix glycoprotein implicated in embryogenesis and tumor progression. The Cinderella Therapeutics Research Corporation, has drafted two phase 2 therapy protocols:

1. IT-radiolabeled IgM for patients with a recurrent Glioblastoma Multiforme (GBM)
2. IT-radiolabeled IgM for patients with a locally advanced cancer of the exocrine pancreas.

Both tumor types are positive on immunohistochemistry with two murine IgM clones of Cinderella that are reactive with human recombinant TNC. In other experimental animal models and a single study in human breast cancer patients by De Jager et al, almost 10% of the IT administered IgM will

translocate from tumor primary to draining lymph nodes by way of fenestrations in lymph vessels.

Figure 3. Low and High magnification of a formalin fixed GBM biopsy stained with a murine anti- human TNC IgM clone of Cinderella

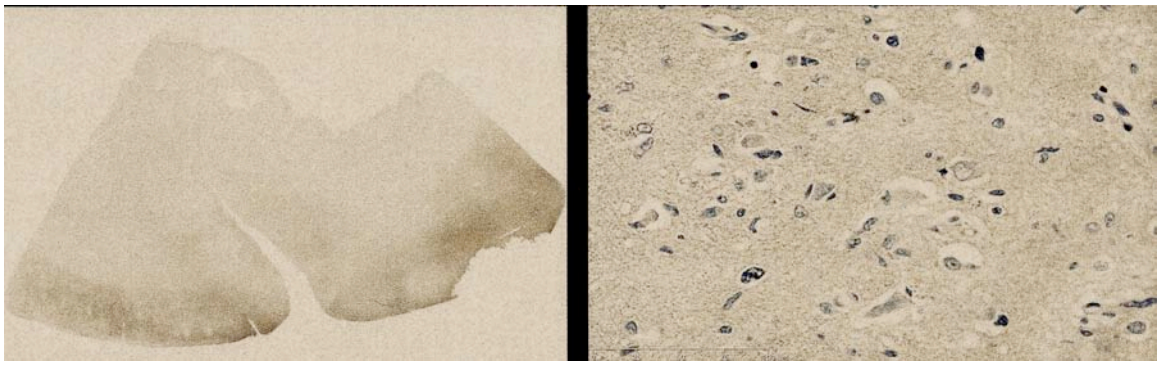
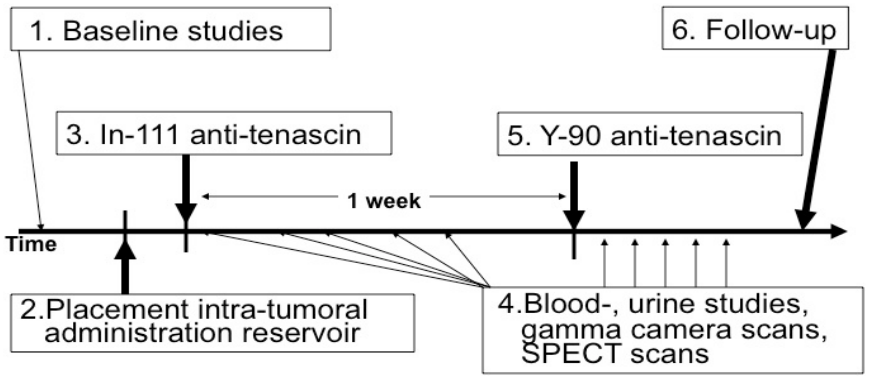


Figure 4 Study schema for patients with GBM recurrence



The first 6 days after IT **In-111** labeled anti TNC IgM the patient has 5 sequential whole body gamma camera or SPECT scans, and provides blood and urine samples, i.e. a complete pharmacokinetic picture and biodistribution of the RIC in the patient under study is obtained. Only if more than 85% of the RIC is retained in the tumor mass, will the patient

receive IT **Y-90** labeled anti TNC IgM. This will deliver the protocol prescribed radiation dose in Gy per cc tumor. Depending on the dose administered the patient will have a high chance to get a beneficial tumor response.
The proposed Imaging and Therapy protocols will facilitate clinical-decision-making by:

1. **Staging** IgM reactive tumor volume in cc's (**3D**), based on SPECT reconstructions instead of by largest **1D** tumor diameter on MR or CT image.
2. **Evaluating tumor response** in percent change in IgM-reactive **3D** volume calculated from pre- and post-treatment IT In-111 TNC-IGM SPECT scans instead of **2D** Response Evaluation Criteria in Solid Tumors (RECIST).
3. **Each** patient receives **Targeted Therapy** with complete '*pharmaco-vigilance'.* Hopefully this will lead to simplified and *cheaper* applications of c-GMP and c-GLP recommendations for R&D of IT-IgM RIT in the near future.

Summary

When IT radiolabeled IgM reactive with TNC indeed shows the anticipated improved local regional control of solid tumors others might become convinced that R&D of stepchild drugs should be investigator driven clinical research. This would resolve some of the lingering negative aspects of 'Doctor Dilemmas' and fulfill Cinderella's mission to bring promising, but not profitable drugs rapidly to patients for an affordable price.