Progress in Anti-polyamine Drug Development/Chemotherapy vs. Protozoan-caused Diseases: The DFMO Story
Submitted by Cy Bacchi

About 1974, I began working with an enzyme called NAD-linked glycerophosphate dehydrogenase in African trypanosomes. We had a difficult time purifying it, and in the process found it was stimulated by Mg^{++} and that we could replace the Mg^{++} with spermine or spermidine. I was prodded in this direction by my former mentor, Seymour Hunter and my late cousin, Edward Ciaccio, Professor of Pharmacology at Hahnemann Medical School. The difficulty in purification of GPDH and its liability arose from the fact it was enclosed in cytoplasmic organelles called glycosomes which Fred Opperdoes demonstrated several years later. At that time I was invited to the pacific Northwest Polyamine Conference (1976) during which I had the good fortune to meet Seymour Cohen. Seymour took me under his tutelege and helped me with my initial studies on quantitation of polyamines in *T. brucei* and the insect trypanosomatids *Crithidia a*nd *Leptomonas*. He inspired me and helped me in many ways.

I started attending Gordon conferences on Polyamines and in 1979 met Peter McCann, then a research scientist with Richardson-Merrell. I asked Peter for some of the new putative anti-tumor agent, DL-α-difluromethylornithine and he responded by sending 25 g – a major amount for that time. My colleague, Henry Nathan and I began dosing *T. brucei* infected mice with 2% DFMO in the drinking water for 3 days 24 h. after infection. To our amazement, the treated mice survived and were cured. We repeated the experiment three times before I called Peter and let him know the news. Al Sjoerdsma, head of the now Merrell-Dow Pharmaceuticals Research Institute, Peter, Seymour Hutner, Henry, and I published our findings in Science in 1980, and the clinical studies ensued.

Initial studies were done by Simon von Nieuwenhove in the Sudan in 1981, through the auspices of WHO and Merrell-Dow. The drug was given orally at 400 mg/kg/day – 4x/day for 2 weeks. Despite problems with diarrhea, ototoxicity and hair loss, DFMO cured most patients, even patients with late-stage disease. Shortly thereafter, the Dutch physician, Henri Talman cured a woman who was initially deeply comatose, with i.v. DFMO dosing. He later coined the term, “the resurrection drug” for its ability to be effective late in the disease.

From these initial clinical trials, more organized studies began, which resulted in the emergence of an i.v. dosing regimen (400 mg/kg/day, 4x day for 1 – 2 weeks). My greatest personal career thrill at this point was meeting Simon Van Nieuwenhove in the back of the Kenyatta Center in Nairobi – we talked for, it seemed, hours about the scientific and clinical work surrounding DFMO.

However, during the 1990’s because of the difficulty of i.v. administration of DFMO, and above all, its expense of ~ $700 per patient, as well as the reluctance of Marion-Merrell –Dow to produce DFMO for essentially a non-profit purpose, its availability and use became restricted, At last count, about 4000 patients had received DFMO, with an overall cure rate of > 90%.

In 2000, a curious thing happened in the world of cosmetic and beauty products. Bristol-Meyers-Squibb began marketing a product called Vaniqua, a prescription depiliatory agent. Most interesting, the active agent in the cream was 18% wt/vol. DFMO, supplied by Aventis (the sequel to Marion-Merrell-Dow). The story of Dr. Michaleen Richer, medical Coordinator of the International Medical Corps, based in Nairobi then appeared: Micky had worked in the Sudan in Simon Van Nieuwenhove's former clinic and her story of the lack of DFMO for clinical use in sleeping sickness was covered on CBS by "60 Minutes". In an amazingly short time, Aventis responded to this negative publicity by arranging to supply 60,000 doses of DFMO/year for 5 years (through Bristol-Meyers-Squibb) and donating $25 million to sleeping sickness research. Since Aventis had taken over the remnants of May and Baker and Rhone-Poulenc, they agreed to continue the supply of the standard trypanocides melarsoprol and pentamidine for 5 years. The production of both of these agents was in danger of being eliminated.

WHO is starting new clinical trials in the Congo. It is going back to oral administration because it is needed in rural settings and the i.v. form of administration can only be given in a hospital setting. Only ~ 10% of gambiense-infected patients receive the i.v. formulation. WHO is therefore attempting a new trial giving DFMO orally to determine the maximum tolerated dose and to see whether it is effective in ≥ 80% of treated patients. If the criteria are met, then WHO would file for registration (presumably as a new clinical regimen). If this fails, WHO will consider combination studies, probably with Nifurtimox. Eflornithine will be dissolved in water and taken as a drink. Fulcrum, a CRO (Contract Research Organization) is helping WHO in working out an approach to the French Regulatory authorities for oral DFMO. A Phase II study would then be done in the Congo. WHO has assembled a product development team for this work and a parallel one would be set up for Nifurtimox. Aventis has continued to supply DFMO and will transfer technology to a company in India and another in Taiwan. WHO is uncertain of the supply of DFMO after the 2006, but Aventis may also be taken over/merge with another company (Sanofi or Novartis).

Recently, Gene Gerner and Associates published their findings concerning the ability of D- and L- forms of DFMO to inactivate ODC. The probability of DFMO-ODC complex formation is 20x greater for L-DFMO, but the rate of irreversible inactivation of ODC is similar for both entantiomers. There has been one published report of L-DFMO inducing ototoxicity at lower doses than the D-form. Thus the possibility of using the D-form for lower toxicity exists.

The issues still remain as to overall cost of producing pure D- or L- DFMO. The major problem with oral DFMO was an osmotic diarrhea, which made for significant non-compliance and reduced overall efficacy below that of i.v. DFMO (85% vs. 99%, respectively).

Meg Phillips is currently studying pure D- and L- forms of DFMO vs. trypanosome ODC to determine whether the D-form has sufficient activity.