

Material Transfer Agreement

DNDi

1, Place St Gervais
CH-1201 Geneva
Switzerland

and

Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

Relative to: a series of nitroimidazoles from the laboratories Pharmaceutical Sciences Research Center and their evaluation as antitrypanosomal drug candidates

I BACKGROUND

The Drugs for Neglected Diseases initiative (DNDi) is a not-for-profit organisation established in 2003 in partnership with Médecins Sans Frontières, Fiocruz in Brazil, the Indian Council of Medical Research, Institut Pasteur in France, the Ministry of Health of Malaysia, and the Kenya Medical Research Institute, with WHO/TDR as a permanent observer. DNDi's goal is to develop effective, safe, affordable and field-adapted drugs to address the needs of patients suffering from the most neglected communicable diseases. Priority diseases include trypanosomiasis (sleeping sickness and Chagas disease) and leishmaniasis. In addition to mobilising and coordinating discovery research to identify new leads and candidate drugs for these fatal diseases, DNDi is also exploring opportunities to piggyback on existing drugs or compounds under development for other indications, for instance the nitroimidazoles or related nitro-compounds.

During 2004, DNDi performed a literature/patent review of past and ongoing research activities on Megazol like molecules. The aim of the study was to investigate whether there remains a promising strategy to find a new drug candidate with a better activity/toxicity profile. Megazol, 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole, is a potent orally active trypanocidal compound which showed promise as a drug candidate against Chagas disease and Human African Trypanosomiasis (HAT). However, its further development was discarded for toxicity (mutagenicity) reasons.

Through this exploratory work, DNDi could identify in different research groups several series of existing nitroheterocycles with interesting properties, including compounds from the laboratories of the Pharmaceutical Sciences Research Center of **Tehran University of Medical Sciences**.

II PURPOSE

In order to assess whether any of the identified compounds could represent possible antitrypanosomal drug candidates, DNDi has undertaken a targeted evaluation of each of the identified series, including Dr Foroumadi's compounds from Pharmaceutical Sciences Research Center of **Tehran University of Medical Sciences**.

For this, DNDi has proceeded to experimentally assess and compare the trypanocidal activity of the identified compounds in well established *in vitro* models. Those showing potent and selective activity *in vitro* will subsequently be tested *in vivo* for their capacity to cure or at least reduce the parasitemia. For this research part, DNDi has concluded a service agreement with the group of Professor Reto Brun at the Swiss Tropical Institute (STI) in Basle (Switzerland), which is the reference laboratory for *in vitro* (*T. brucei* and *T. cruzi*) and *in vivo* (*T. brucei*) trypanocidal activity testing. In parallel, DNDi wishes to look at

the toxicity profile of the active trypanocidal compounds, in particular to assess possible genotoxicity as this is a common problem with the nitroimidazole class of molecules. For this, DNDi is working with a regulatory toxicology expert to set up an appropriate strategy for toxicity testing. This experimental part will be outsourced to a specialised contract research organisation.

So far Dr Foroumadi has kindly provided DNDi with milligram quantities of 150 different compounds, which are currently undergoing testing in the *in vitro* assays cited above. Selected compounds with good activity will subsequently be tested *in vivo* (an estimated 5-10) and for genotoxicity (an estimated 5-10), for which quantities of 50 mg and 2 g respectively will be needed.

The Pharmaceutical Sciences Research Center of **Tehran University of Medical Sciences** has committed to support the production of sufficient quantities of the selected compounds. DNDi finances and manages via outsourcing the biological activity testing as described above.

It is expected that this exploratory evaluation phase will lead to the identification and selection of one or a few lead compounds or drug candidates among all tested from different sources from **Tehran University of Medical Sciences**, on which DNDi aims to build a more advanced drug development programme for trypanosomiasis. This evaluation phase is expected to be concluded in the course of 2006.

III THE PRINCIPLES

If any lead molecule is identified through this exploratory project within the series of Dr Foroumadi, its further development would be carried out under separate agreement on mutually acceptable terms and conditions.

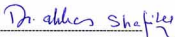
In such case, DNDi will secure access to the candidate compounds in a way that maximally serves the goal of making available affordable new treatments for neglected patients, along the lines set out in the DNDi's intellectual property policy (in annex).

In case it is considered necessary by the Parties to take measures to obtain protection of the intellectual property rights on the results of this collaboration, the Parties agree that DNDi shall take such measures (for instance by filing for patent protection), whereby DNDi agrees to duly acknowledge the contribution of Pharmaceutical Sciences Research Center of **Tehran University of Medical Sciences** in this context by naming the relevant person(s) within the Pharmaceutical Sciences Research Center of **Tehran University of Medical Sciences** as inventor or co-inventor of the relevant invention in the case when patent protection shall be sought. Subject to the obligation of DNDi to comply with the terms and conditions of DNDi's intellectual property policy (pursuant to which DNDi shall not seek to derive revenues from the exploitation of its intellectual property rights), any net profit resulting from the exploitation of the intellectual property rights will be shared equally between the Parties.

**Pharmaceutical Sciences Research Center,
Tehran University of Medical Sciences**

Drugs for Neglected Diseases *initiative*

By:



Name: Abbas Shafiee (Prof. of Chemistry)

Title: Head of Pharmaceutical Sciences Research Center

Date:

By:



Name: Dr Bernard Pécoul

Title: Executive Director

Date: