



UNIVERSITY OF TORONTO
FACULTY OF MEDICINE



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MEDICAL ALUMNI ASSOCIATION AND CREMS-SPONSORED
DR. ELVA MAY ROWE FUND
INTERNATIONAL HEALTH SUMMER RESEARCH PROGRAM
2017 SUPERVISOR PROJECT INFORMATION FORM

If you wish to act as a Supervisor for a first or second year University of Toronto medical student wishing to conduct a research project abroad between June and August 2017, please complete the below form with as much detail as possible.

PLEASE PROVIDE A COPY OF THE ON-SITE SUPERVISOR'S CV. THIS IS REQUIRED FOR THE ADJUDICATION PROCESS.

****Submit this form to crems.programs@utoronto.ca by the deadline of Thursday January 5, 2017.****

PART A: Supervisor and On-Site Supervisor Contact Information

UofT Researcher:	Dr. Nancy Olivieri
Email Address:	nancy@hemoglobal.org
Telephone:	647-299-6935
Mailing Address:	Toronto General Hospital 200 Elizabeth Street, EN 13-222, Toronto, Ontario Canada M5G 2C4
Department:	Medical Oncology and Hematology
Degree (MD, PhD, MD/PhD):	MD, MA, FRCPC
SGS Appointment/where?:	Institute of Medical Sciences
Selected Publications (3 most recent and relevant to the project the student will be working on):	Premawardhena A, Fisher CA, Olivieri NF, de Silva S, Arambepola M, Perera W, O'Donnell A, Peto TE, Viprakasit V, Merson L, Muraca G, Weatherall DJ. Haemoglobin E beta thalassaemia in Sri Lanka. Lancet 2005; 366:1467-70. Olivieri NF, Thayalsuthan V, O'Donnell A, Premawardhena A, Rigobon C, Muraca G, Fisher C, Weatherall DJ., Emerging insights in the management of hemoglobin E beta thalassaemia. Ann N Y Acad Sci. 2010; 1202:155-7. Mettananda S, Gibbons R, Higgs D. α -Globin as a molecular target in the treatment of β -thalassaemia. Blood 2015; 125: 3694-701
Name of On-site Supervisor:	Dr. Anuja P Premawardhena
Location of placement (Name of Institution/hospital; City; Country):	Professor in Medicine, Department of Medicine, University of Kelaniya Sri Lanka; Consultant in charge: Adolescent & Adult Thalassaemia Care Unit, North Colombo (Teaching) Hospital Ragama, Sri Lanka
Email Address:	premawa@hotmail.com
Telephone:	
Degree (MD, PhD, MD/PhD):	M.B.B.S, M.D M.R.C.P (London) 2001 D.Phil (Oxon) 2002



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	FRCP (London) 2008 FCCP (Sri Lanka) 2010
Area of Medicine of the Research Project (2 keywords):	Thalassaemia, Global Health

PART B: PROJECT INFORMATION

Project Title (this can be modified later, but we would like to have working title from the start):
Evaluation of patients with thalassemia at increased risk of cardiac disease in Sri Lanka

Provide background information on the project and program/institution; max 500 words:

This student project will collect data to further study of the central and critical question in thalassemia: why is iron-induced cardiac disease, the commonest cause of mortality in transfusion dependent thalassaemia patients in higher-income countries, less frequently observed in thalassaemia patients in areas where transfusion practices result in administration of less blood? Recent work has shown that the risk of cardiac iron overload in thalassemia may be predicted by a newly-identified metric: the difference between the iron loading rate (“Iron Loading Rate”) from blood transfusions, and the activity of red cell precursors to utilise (transferrin-bound) iron (Erythron Transferrin Uptake), which is measured using the plasma concentration of soluble transferrin receptors (sTfR). In patients in whom the rate of *Erythron Transferrin Uptake* (ETUR) minus the *Iron Loading Rate* (ILR) is less than <0.21, the risk of cardiac iron deposition appears to be increased by nearly 50-fold (Garbowski et al Haematologica 102(10) 1640-1649 (2017), a higher predictive value than any other factor identified. Measurement of cardiac iron in large numbers of patients with thalassemia is problematic in Sri Lanka; hence we wish to identify the patients at most risk: ie those in whom the rate of blood transfusion (ILR) exceeds iron utilisation by the erythron, the erythron transferrin uptake (ETUR), according to the formula

- $ETU[\mu\text{mol Fe/L plasmaday}] = 0.013 * sTfR1[\mu\text{g/L}] + 2.25$

By decreasing the transfusion rate in patients identified as high risk from the above metric, the risk of cardiac iron loading and hence mortality can be reduced. To screen for patients at risk the medical records of approximately 1000 patients with thalassemia, primarily thalassemia major and Hemoglobin E thalassemia, in two centers in Sri Lanka, will be assessed for iron overload (estimated by serum ferritin concentration or quantitated by liver iron concentration) and for rates of *Erythron Transferrin Uptake* and *Iron Loading Rate* (ILR). Students will calculate the rate of blood transfusion (mg/kg body wt iron/day) from the number of units of blood transfused in the previous 12 months and the patient’s weight, all recorded in the patient’s chart Blood will be drawn for measurement of soluble transferrin receptor at



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the same time as serum ferritin. The ETUR will be derived as recently described from the transfusion iron loading rate and the soluble transferrin receptors which will be determined in each patient, and the odds ratio for cardiac iron deposition will be calculated for patients with ETUR < or > than 0.21. This odds ratio will be compared with other risk factors such as liver iron, serum ferritin control and use of chelation.

What, if any, second language is required for the student to successfully complete this project?
Fluency/understanding of Sinhala or Tamil will be useful but not required.

Is this project for 1 or 2 students to complete?

1 2

Two students sharing the work has worked well in similar projects. There are a large number of patient charts, as well as a wealth of associated clinical material and large clinics, so that this project offers sufficient work for two students.

How long have you worked with the on-site supervisor and briefly describe your working partnership:

My clinical and research teams have worked in Sri Lanka for 22 years. My primary research partner in this work has been Professor Sir David Weatherall, FRS (the world's leading authority in thalassemia) at the University of Oxford, UK, with whom I continue actively to work. The proposed local supervisor, Dr Anuja Premawardhena, trained in basic and clinic research and hematology at the Weatherall Institute of Molecular Medicine, University of Oxford, UK where he received his D. Phil in 2002. I have worked with and continue to work with Dr. Premawardhena before and following his staff appointment in Sri Lanka. We meet and discuss our work on each field trip to Sri Lanka, of which three were conducted in 2017.

Have you visited the city/town where the medical student will be placed? If yes, when was your last visit?

Yes, to both Ragama and Kurunegala. I have worked in Sri Lanka for 22 years. I lead at least three field trips per year to the country, the most recent in June 2017. I will be visiting Sri Lanka in summer 2018 to provide additional support to the students, if funded.

Student's roles/responsibilities in bullet form (Please be as specific as possible):

- Students should develop a deep and broad understanding of the clinical and laboratory aspects of thalassemia including the complications of iron loading and approach to treatment;
- Students will accompany Dr. Premawardhena and participate in rounds and clinics with daily interactions with thalassemia patients aged approximately 5-50 years;
- Students will "shadow" other physicians, in the hematology and other clinics, to gain appreciation and understanding of hematology and tropical disease such as dengue common in Sri Lanka;
- The research project will be specifically directed at evaluation of transfusion regimens in all patients (approximately 1000) in two thalassemia units (The Adolescent & Adult Thalassemia Care Unit, North Colombo (Teaching) Hospital Ragama, Sri Lanka; the National Thalassemia Center, Kurunegala).
- Students will at both sites conduct chart reviews of all available thalassemia patients receiving any frequency of transfusions to record serum ferritin concentration; liver iron concentration; rate of transfusion; pre-transfusion hemoglobins; and other endpoints to be outlined and will assist with data entry
- Students will write up their findings with my and Dr. Premawardhena's assistance.

Is this project for a specific student, or will you interview and select an interested student who would contact you directly for this

For a specific student. Name of student:

For whichever student is chosen after interview



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<p>opportunity? <i>Note: All supervisor/student applications will be adjudicated by a panel of faculty, given a score, and ranked based on the score given. Funding will be based on ranking.</i></p>	<p>We would welcome any students for this project. We hope that two can be funded in parallel on this project.</p>
<p>If human subjects are involved, has Ethics been obtained? <i>(Note: Written proof or an email indicating protocol approval may be requested prior to the student's arrival at on-site location)</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p> <p style="padding-left: 150px;">Yes</p>

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Attached