ATTACHMENT A

STATEMENT OF WORK
ALLOCATION OF EFFORT
STTR 1R41CA217421-01A1
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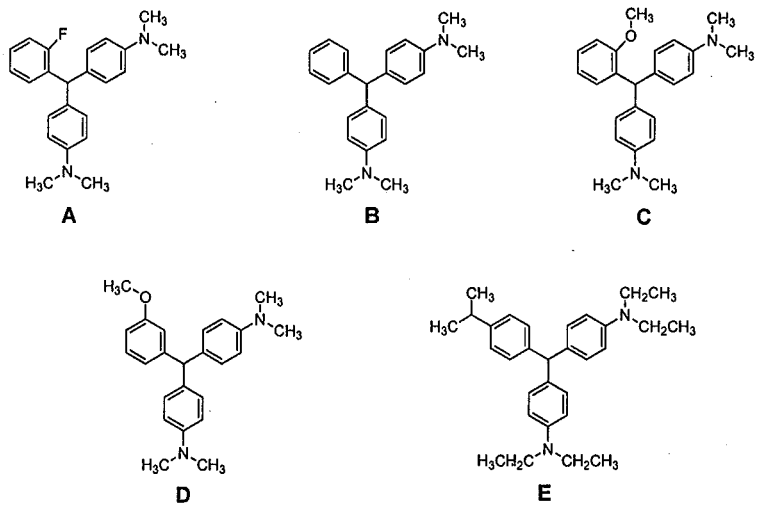
This Attachment describes the tasks to be performed, the deliverables to be provided, responsibility, reporting requirements, and a timeline of efforts at Heuris and Duke to achieve the goals of the STTR project.
The tasks follow the Specific Aims and Milestones which appear in the funded STTR application.
Tasks which are the responsibility of Heuris appear as **red font**, and tasks which are the responsibility of Duke appear as **blue font.** Tasks for which both Heuris and Duke are responsible appear as green font.

Specific Aim 1: PRESAGE dosimeter formulation. The research to achieve this Specific Aim has two components, both of which entail the preparation of various PRESAGE formulations with modifications of leuco dyes, catalysts, and additives in a polyurethane matrix characteristic of the PRESAGE dosimeter.
Task 1: This component relates to the development of a **REUSABLE** PRESAGE dosimeter of clinically relevant volume (0.5-2 kg) which is capable of high-resolution recording of an incident radiation field by optical changes within the dosimeter caused by the interaction of incident radiation and components within the dosimeter. The optical changes must persist for a time sufficient for accurate evaluation of the dosimeter by the scanning system. The formulation is designed so that the optical changes will fade or caused to be erased under conditions determined by the research efforts conducted in Task 1. The successful formulation will provide a dosimeter which can be irradiated, measured, and erased, and which can be reused a number of times. It is anticipated that several dyes will be prepared and incorporated into PRESAGE formulations with varying amounts of catalysts and additives. Currently, the plan is to synthesize compounds **A-E** for evaluation in **REUSABLE** PRESAGE formulations. During the course of the project, it may become clear that structural modifications of the projected dye molecules will be necessary to achieve optimal results.



Triarylmethane leuco dyes to be synthesized and evaluated in REUSABLE formulations in Task 1.

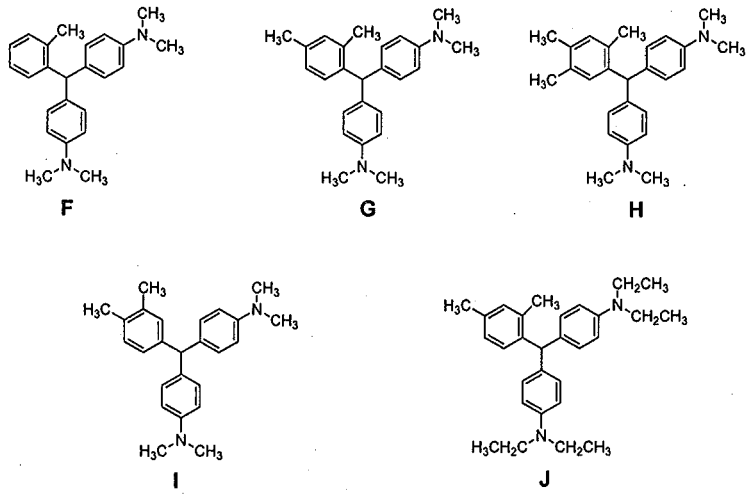
Task 1.1. Initially the formulations under study will be cast into 1 cm. optical cuvettes for ease of analysis. The stability of the optical information captured after radiation for each formulation will be evaluated by comparing the absorbance of transmitted light at the appropriate wavelength at nine time points. Each formulation will be stored at three temperatures post-irradiation. Five cuvettes of each formulation for study under the three temperature conditions will be cast, requiring the preparation of fifteen cuvettes for each formulation. The best REUSABLE formulation will be selected for further development.

Task 1.2. The selected formulations will then be appropriately scaled to allow molding into dosimeters of clinically relevant size which will be irradiated and scanned by the Duke team.

Task 1.3 The clinical dosimeters will be irradiated with relatively simple well characterized treatment plans (e.g. a 4-field box created with a maximum dose of 5 Gy). The simplicity of the plan is also practical for accurate, reproducible set-up for the two different formulations. The suitability of the PRESAGE dosimeters will be evaluated through any combination of line profiles, dose-maps, a 3D gamma map, and calculations between the measured and known 3D dose distributions. 3D gamma passing rates will calculated in Computational Environment for Radiochemical Research (CERR) against the Eclipse-calculated treatment plan. Calculations will be performed under 3 sets of gamma criteria with a 5% maximum dose threshold: 5%/2mm, 3%/3mm, and 3%/2mm. The criteria of 3%/3mm with a 10% maximum dose follow recommendations of Task Group 119 IMRT Commissioning Tests (TG119).

Task 1.4 The best formulation will be selected by mutual agreement of the Duke and Heuris teams. It is anticipated that the criteria for selection shall include ease and expense of manufacture, transient stability of the data contained within the irradiated dosimeter to allow accurate representation of the incident radiation field, conditions required to cause the dosimeter to be reusable, and the number of times the dosimeter can be reused.

Task 2: This component relates to the development of a **STABLE** PRESAGE dosimeter of clinically relevant volume (0.5-2 kg) which is capable of high-resolution recording of an incident radiation field by optical changes within the dosimeter caused by the interaction of incident radiation and components within the dosimeter. The optical changes may not disperse, fade, or otherwise change under reasonable handling, storage, and shipping conditions. The stable PRESAGE dosimeter is intended to be used in the measurement and validation of a radiation therapy treatment plan at a clinical facility and subsequently shipped to a facility capable of scanning the irradiated dosimeter and rendering a three-dimensional image to be analyzed by clinicians at the treatment facility. The optical information contained within the irradiated stable dosimeter should therefore remain unchanged during the time required to process, ship, and evaluate the dosimeter. The formulation is designed such that will not change to a clinically significant extent during storage, shipment, and scanning under reasonably attainable conditions determined by the research efforts conducted in Task 2. It is anticipated that several dyes will be prepared and incorporated into PRESAGE formulations with varying amounts of catalysts and additives. Currently, the plan is to synthesize compounds **F-J** for evaluation in **STABLE** PRESAGE formulations. During the course of the project, it may become clear that structural modifications of the projected dye molecules will be necessary to achieve optimal results.



Triarylmethane leuco dyes to be synthesized and evaluated in STABLE formulations in Task 1.

Task 2.1 Initially the formulations under study will be cast into 1 cm. optical cuvettes for ease of analysis. The stability of the optical information captured after radiation for each formulation will be evaluated by comparing the absorbance of transmitted light at the appropriate wavelength at nine time points. Each formulation will be stored at three temperatures post-irradiation. Five cuvettes of each formulation for study under the three temperature conditions will

be cast, requiring the preparation of fifteen cuvettes for each formulation. The best STABLE formulation will be selected for further development.

Task 2.2 Selected formulations will then be appropriately scaled to allow molding into dosimeters of clinically relevant size which will be irradiated and scanned by the Duke team.

Task 2.3 The clinical dosimeters will be irradiated with relatively simple well characterized treatment plans (e.g. a 4-field box created with a maximum dose of 5 Gy). The simplicity of the plan is also practical for accurate, reproducible set-up for the two different formulations. The suitability of the PRESAGE dosimeters will be evaluated through line profiles, dose-maps, a 3D gamma map, and calculations between the measured and known 3D dose distributions. 3D gamma passing rates will calculated in Computational Environment for Radiochemical Research (CERR) against the Eclipse-calculated treatment plan. Calculations will be performed under 3 sets of gamma criteria with a 5% maximum dose threshold: 5%/2mm, 3%/3mm, and 3%/2mm. The criteria of 3%/3mm with a 10% maximum dose follow recommendations of Task Group 119 IMRT Commissioning Tests (TG119).

Task 2.4 The best formulation will be selected by mutual agreement of the Duke and Heuris teams. It is anticipated that the criteria for selection shall include ease and expense of manufacture and conditions required to maintain the integrity of the information contained within the irradiated dosimeter during storage, shipping, and scanning.

Specific Aim 2: Development of a commercially viable Duke Integrated Optical-CT (DIOS) Scanner. This portion of the funded research has three components, two of which involve the optimization and characterization of a DIOS scanner, and preliminary benchmarking and validation of the scanner to be capable of delivering high-quality images truly representative of complex radiation fields captured by a PRESAGE dosimeter in the treatment planning for radiotherapy. The third component is the optimization of the design and preparation of a solid polyurethane block containing a cavity into which a PRESAGE dosimeter will be fitted. The goal of this Aim is the successful integration of the block, dosimeter, DIOS scanner, and related software.

Task 3. Development of the solid refractive index matching block. The first solid refractive index matching solid blocks have provided promising results. In this Task, ways to improve the manufacture of the block will be investigated. Critical parameters such as the volume of the block with respect to the volume of the dosimeter to be scanned, the nature of the lensing surfaces of the block, including the degree of curvature and the potential need for polishing or coating of the lensing surfaces, and the optimal shape of the PRESAGE dosimeter to be scanned and therefore the cavity built into the block will be determined. Also, the nature and amount of lubricant to facilitate the rotation of the dosimeter within the block will be determined.

Task 3.1. Determination of the prototype refractive index matching block and cavity parameters. Heuris and Duke will review the methods to design and produce high optical quality polyurethane blocks best suited for optimal performance in the DIOS scanner. Included in this determination will be the shape of the optimal PRESAGE dosimeter and the nature of the lubricant.
Task 3.2. Production of refractive index matching blocks. Heuris will manufacture five blocks to specifications agreed to in Task 3.1. The evaluation of the refractive index matching blocks fall under Task 4 and Task 5.
Task 4. Optimization and characterization of the DIOS prototype scanner. We are experienced in optimizing and characterizing optical-CT scanning systems. We will follow the general methods and experimental approaches outlined in our prior work characterizing the DLOS scanner. DIOS commissioning will involve determining the dynamic range, spatial resolution, noise, temporal, and other characteristics of the light source and imaging components. This will include:
Task 4.1. Construction and experimental evaluation of optimized DIOS scanner. A limited number of options will be explored to determine optimum light source and scanner geometry configuration in combination with optimal shaped dry-tank.
Task 4.2. Investigation of general utility of the light-collimating tank including flood field uniformity, noise, and consistency.
Task 4.3. Investigation of geometric accuracy of the scanner in 3D through comparison of x-ray-CT and optical-CT of needle finger phantoms.
Task 4.4. Investigation of stray-light contamination and artifacts through light block images.
Task 4.5. Investigation of noise and artifacts in reconstructed 3D images.
Task 5.1. Benchmark DIOS performance. Investigation of capability for 3D dosimetry and benchmarking will be performed by cross-comparison of dose maps acquired on the same irradiated dosimeters with both the DLOS and DIOS scanners. Further comparisons will be made with eclipse for simple dose distributions. Benchmarks will ideally establish the expected level of agreement between DIOS and DLOS and eclipse in terms of gamma passing rates at common criteria levels (e.g.3%,3mm). Benchmarking tests will be performed on the combined DIOS/PRESAGE system to establish baseline dosimetric performance. The tests will consist of delivering simple radiation treatments to PRESAGE dosimeters, and comparing the measured 3D relative dose distributions with the known gold standard. The gold standard distribution will be obtained from machine beam-data or the treatment planning system (TPS). All studies will use standardized procedures to ensure consistency.

Reporting requirements. In order to facilitate a Final Research Report to be submitted to NCI at the end of the Phase I STTR period, a monthly written review of the efforts of Heuris and Duke will be generated. At the end of each calendar month, beginning November 30, 2017, Duke will submit to Heuris a summary of the results of the research toward completion of the Specific Aims delineated herein. In turn, Heuris will prepare a monthly Project Status Report of the results

of the research efforts of both Heuris and Duke. The Project Status Report will be sent to Dr. Oldham for his review and comments for incorporation into the document. Once the Status Report is agreeable to both Heuris and Duke, it will be archived pending the preparation of a Final Report at the end of the Phase I period.

Deliverables. The Table below outlines the tasks, responsibilities, milestones, and deliverables.

Task	Start Date	Completion Milestone	Responsibility	Deliverables
1.1	11/1/2017	3/1/2018	Adamovics	Cuvette Study of Reusable Formulations
1.1	----	3/1/2018	Adamovics	Selection of best Reusable Formulation
1.2	2/1/2018	6/1/2018	Adamovics	Scale best Reusable Formulation to Clinically Relevant Volume. Provide overview of dosimeter preparation.
1.3	3/1/2018	6/1/2018	Oldham	Scanning evaluation of Reusable PRESAGE Dosimeters
1.4	----	6/1/2018	Adamovics and Oldham	Selection of the Reusable PRESAGE formulation
2.1	1/1/2018	4/1/2018	Adamovics	Cuvette Study of Stable Formulations
2.1	----	4/1/2018	Adamovics	Selection of best Stable Formulation
2.2	4/1/2018	5/1/2018	Adamovics	Scale best Stable Formulation to Clinically Relevant Volume
2.3	5/1/2018	6/1/2018	Oldham	Scanning evaluation of Stable PRESAGE Dosimeters
2.4	----	6/1/2018	Adamovics and Oldham	Selection of the Stable PRESAGE formulation
3.1	9/1/2017	4/1/2018	Adamovics and Oldham	Define Solid Block Parameters
3.2	9/1/2017	6/1/2018	Adamovics	Manufacture of five (5) solid blocks. Provide overview of solid block preparation.
4.1	1/1/18	5/1/18	Oldham	Construct optimized prototype DIOS
4.2	1/1/2018	6/1/18	Oldham	Flood field uniformity and consistency
4.3	1/1/2018	6/1/18	Oldham	Geometric accuracy
4.4	1/1/2018	6/1/18	Oldham	Stray light quantification
4.5	1/1/2018	6/1/18	Oldham	Noise and artifacts
5	4/1/2018	9/1/18	Oldham	Preliminary characterization and benchmarking of the overall performance of the scanner for 3D

				dosimetry.