

Plan Overview

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Title: Development of Pet-1 as a small molecule inhibitor of the CDP-ethanolamine Kennedy pathway with therapeutic potential for Non-Small Cell Lung Cancer

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Project abstract:

Lung cancer is one of the most lethal cancers in the world and development of new drugs is essential for the control of this disease. Interfering with membrane phosphatidylethanolamine (PE) synthesis is an attractive novel strategy for rational drug design in lung cancer. The main route of PE synthesis by the CDP ethanolamine Kennedy pathway is regulated by CTP: phosphoethanolamine cytidylyltransferase (PCYT2). In the present study we will synthesized a new antitumor lead (called Pet-1) a phospholipid ether derivative, Pet-1, which is a novel inhibitor of PCYT2 and the CDP-ethanolamine Kennedy pathway. PCYT2 knockout was produced using CRISPR-Cas9 and validated its importance in development of lung cancer. We have recently developed a small molecule, named CHY- 1, as potential anticancer drug candidate against lung cancer. Most importantly, CHY-1 blocks Pcyt-2 leading to the reduction of PE intracellular levels. Also, it reduces autophagy flux in the H460 and A549 cell lines, which is a remarkable effect. In addition, CHY-1 produces an endoplasmic reticulum (ER) stress leading to the activation of unfolded protein response (UPR) systems and increased immunogenicity of tumor cells both in vitro and in vivo.. Importantly, CHY-1 has reduced the tumor volume in NSCLC animal model. These data qualify CHY-1 as a novel inhibitor of PCYT2 and the CDP-ethanolamine Kennedy pathway operating through multiple mechanisms for cell death including the inhibition of autophagy, the induction of ER stress and the immunogenic cell death. Thus, as the technological feasibility regarding CHY-1 has been provided, it can be considered as a prototype/lead compound to follow the step of lead optimization for developing novel drug

candidates to treat NSCLC. The lead compound (Pet-1) was conceived based on a well-established, interactive, and multidisciplinary process, regarding the development and structural optimization of a template, integrating computer-aided drug design (CADD), organic chemistry, and pharmacological evaluation (biological assays *in vitro* and *in vivo*). Overall, this project aimed to the lead optimization of Pet-1 as a Pcyt-2 inhibitor, synthesis (drug file), synthesis scale-up, and pharmacological evaluation *in vitro* and *in vivo*. A highlight of this study is the evaluation of Pet-1 effects using the lung-on-a-chip as a proof-of-concept. This human “breathing lung-on-a-chip” microdevice provides the capabilities to reconstitute three-dimensional microarchitecture, dynamic mechanical activity, and integrated physiological function of the alveolar–capillary interface. Thus, this *in vitro* toxicological and pharmacological assay increases the prediction of Pet-1 *in vivo* outcome.

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Development of Pet-1 as a small molecule inhibitor of the CDP-ethanolamine Kennedy pathway with therapeutic potential for Non-Small Cell Lung Cancer

Coleta de Dados

Que dados serão coletados ou criados?

The data concerning the antitumor effects of Pet-1 in vitro and in vivo will be analysed and organized in graphs, aiming to clarify their potential anticancer effects

All the data will be stored as tables and graphics (.doc or .xls format).

Como os dados serão coletados ou criados?

Data will be collected by performing biological assays: celular, molecular, biochemical and animal model

analyses, according to regular methodologies largely described in the literature. Negative and positive controls from each assay will be performed. In addition, the assays will be repeated at least 3 times.

Documentação e Metadados

Que documentação e metadados acompanharão os dados?

Tables, graphics, and figures will be made to ensure that everyone with access to the data, could read and interpreted it in the future. The statistical analyses will be performed in appropriate fashion. Also, everyone could reach some missing information by requesting them to the PI of the project

Ética e Conformidade Legal

Como você administrará qualquer questão ética?

The present proposal of investigation are going to use human and murine cell cline. Indeed, the animal models will need to be approved by Ethics Committee.

All the researchers of the laboratory will have access to the data.

Como você vai gerenciar os direitos autorais e os direitos de propriedade intelectual (IP / IPR)?

Processed data will be freely available after the patente done. Raw data will be released after this step.

Armazenamento e Backup

Como os dados serão armazenados e terão backup durante a pesquisa?

During the developement of the project, data will be stored in personal computers and rigid disks, with virtual backups as google drive , for example.

Como você vai gerenciar o acesso e a segurança?

The PI of the laboratory have access to the raw data stored in the hard drive and in the storage clouds. However, to have access to this, the researchers need to ask for the responsible for the project.

Seleção e Preservação

Quais dados são de valor a longo prazo e devem ser mantidos, compartilhados e / ou preservados?

The data will be shared through the academic community in scientific papers after the patente. In addition, researchers who request access to the data will need to formally request this access for the responsible researcher of the project and the identity of the subjects will be warranty.

Qual é o plano de preservação a longo prazo do conjunto de dados?

Data will be made available for how long the institutional repositor exists and the paper indexes in the journals.

Compartilhamento de Dados

Como você vai compartilhar os dados?

The data will be available at any time upon a formal request for the PI of the project.

Existem restrições ao compartilhamento de dados requeridos?

After the patente made, there will be no restrictions on sharing the data.

Responsabilidades e Recursos

Quem será responsável pelo gerenciamento de dados?

The PI will be responsible for this project

Quais recursos você precisará para entregar seu plano?

FAPESP
