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Application of Translational Biology

Collins Green*

Department of Medicine, Nanyang Technological University, Nanyang Ave, Singapore

***Corresponding author:** Email: green_c@gmail.com

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Description

Small Cell Lung Cancer (SCLC) is one of the four major histological types of lung cancer. The incidence of SCLC in developed countries has declined in recent years, presumably because of changes in cigarette composition. In the United States, SCLC is estimated to represent approximately 16% of new lung cancer diagnoses, which equates to approximately 35,000 new cases annually. In underdeveloped countries the percentage of SCLC cases may be higher. SCLC presents with a very large number of genetic alterations, including alterations of tumor suppressor genes, and copy number gains and other somatic mutations in transcription factors, enzymes involved in chromatin modification, and receptor tyrosine kinases and their downstream signaling components. SCLC has a high propensity for early spread and a high initial responsiveness to cytotoxic chemotherapy that is usually followed by rapid development of resistance.

Non-small cell lung cancer (NSCLC) belongs to the most frequently diagnosed cancer entities and is one of the leading causes of cancer related death worldwide. Deregulation of protein synthesis has received considerable attention as a major step in cancer development and progression. Protein synthesis is regulated at multiple stages, including translation of mRNA into proteins. Studies suggest that ribosomal protein synthesis plays a direct role during tumor-initiation. Crucial for this translation process are Eukaryotic Initiation Factors (eIFs), which ensure the correct 80S ribosome assembly. eIFs are linked to the MAPK and the mTOR signalling pathways, which have become major targets in cancer therapy. Mutations or deregulated expression of eIFs influence cell growth and proliferation, and contribute to carcinogenesis. We hypothesized that eIFs represent crossroads for carcinogenesis in lung cancer and might serve as potential biomarker.

With industry increasingly sourcing preclinical drug discovery projects from academia it is important that new academic discoveries are enabled through translation with HTS-ready assays. However, many scientifically interesting, novel molecular targets lack associated high-quality, robust assays suitable for hit finding and development. The power of basic research lies not only in its contribution to knowledge, but also in its potential for translation, adapting and developing work done in the laboratory to create innovative, novel approaches to prevent and control public health threats. The path for translation of basic research findings is a highly iterative and interdisciplinary approach that is often unfamiliar to those in academic environments. The resources and perspectives required to bring a new idea into the realm of products involve collaborative relationships and learning that are, necessarily, elements of the business world. These include elements of establishing investment priorities, marketing, regulatory requirements, and, of course, sustainability of products.

In the past decades, we have gained important insights into the mechanisms of disease and therapy underlying chronic inflammation in Juvenile Idiopathic Arthritis (JIA). These insights have resulted in several game-changing therapeutic modalities for many patients. However, additional progress still has to be made with regard to efficacy, cost reduction, minimization of side effects, and dose-tapering and stop strategies of maintenance drugs. Moreover, to really transform the current therapeutic strategies into personalized medicine, we need validated biomarkers to translate increased insights into clinical practice.

To bridge this gap, the Scottish Universities Life Sciences Alliance (SULSA) established a fund to develop assays to meet quality criteria such as those of the European Lead Factory. A diverse project portfolio was quickly assembled, and a review of the learnings and successful outcomes showed this fund as a new highly cost-effective model for leveraging significant follow-on resources, training early-career scientists and establishing a culture of translational drug discovery in the academic community.

Essentially all patients in any stage receive a doublet combination of etoposide with cisplatin or carboplatin. For the rare patient without nodal involvement, the chemotherapy may follow surgery, and for the patient with nodal disease without distant metastases, a combination of chemotherapy with chest radiotherapy is usually given concurrently. Unfortunately, the duration of effect of these therapies is short and they are not curative in most instances, with 5-year survival rates less than 7%. No major treatment advances have occurred over the past 30 years. Since the approval of topotecan in 1996, the U.S. Food and Drug Administration (FDA) have not approved any new

drugs for the treatment of patients with SCLC. For these reasons SCLC was declared a “recalcitrant” cancer in the United States. However, considerable therapeutic opportunities, including targeted therapies, exist because of recent developments in understanding of the biology and molecular biology of SCLC that are in part due to the new model systems.

Translational Biology

A key initial step for translational biology to succeed in delivering nascent medicines is the identification of high-quality chemical matter that predictably modulates a desired biological effect.

Multiple methods exist for generating or discovering lead compounds but all rely on access to one or more assays that are reproducible and have a capacity or throughput matched to the techniques being employed. The expertise and facilities required creating these high-throughput assays have traditionally resided in pharma companies and lack of access has limited the approaches employed by groups outside of industry. This is particularly evident for life science academics that rarely have the expertise or equipment to carry out HTS on the scale of ≥0.5 million compounds as conducted in large pharma or the ELF.