Promoting precision cancer medicine

Dr Eitan Rubin is dedicating his career to tackling cancer through personalised therapeutics. While discussing his cutting-edge research, he talks about the Worldwide Innovative Networking Consortium in Personalized Cancer Medicine, which continuously inspires him.

What first sparked your interest in oncological research, and precision cancer medicine in particular?

As a bioinformatician, I was looking for research opportunities that would enable me to improve medicine through the computational analysis of medical information, while learning more about biology. In 2010, I joined the Worldwide Innovative Networking (WIN) Consortium in Personalized Cancer Medicine in the hope that it might allow me access to patients’ clinical information. Although this did not occur, joining WIN opened my eyes to the rapid progression in the field of precision cancer medicine. I realised this research area has the most advanced datasets, which combine detailed molecular profiles of tumours and detailed phenotypic information about drug response and final outcome – the kind of data I have always dreamed of investigating.

Can you provide an overview of the research your lab is currently working on?

We have a wide range of projects, all involving the use of computational tools to predict the outcome for an individual cancer patient. Our projects range from basic to practical, and from bench to bedside tools. On the basic side, we are working to understand immune response in tumours. On the practical side, we are taking part in clinical trials; for example, we are involved in one in which drug selection is determined – at least for some of the patients – by a scoring system that we developed based on an algorithm invented at Institute Gustav Roussy, France. Between these extremes, we are establishing tools and protocols for sharing information, evaluating methods for drug efficacy prediction, analysing survival trends and exploring new ways to improve drug choice based on molecular profiling of tumours.

Knowledge linking cancer drugs and potential efficacy biomarkers is in its infancy. How are you improving this knowledge in the open-access knowledgebase for precision cancer medicine (PCM)?

Developing a database in which cancer cases are recorded is actually not that difficult; it requires documenting abnormalities in the tumour, treatment decisions and outcomes in a structured way. The hard part of creating this knowledgebase is motivating the people who have the knowledge to share it. Currently, most efforts focus on collecting and better organising the information that is stored in computers of the clinical centres or health maintenance organisations that treat patients. This approach is based on obligatory data entry: clinicians cannot treat or be reimbursed without entering information into the system. The problem with this approach is that since each centre typically runs its own information system, reorganising it in a standardised format requires major efforts per centre. As a result, current standardisation activities focus on a small number of large centres, offering only isolated examples of the patient populations served.

We are building the PCM Wiki and Knowledgebase to move away from this isolated model and build reward mechanisms that will encourage voluntary contributions, where clinicians and patients contribute information because it is worth their time and effort. The rewards would come in the form of a clinical decision support system and academic credit via a peer-reviewed publication.

Can you provide an insight into the WINTHER clinical trial?

The trial is a bold effort to evaluate the benefits of precision medicine in advanced cancer. Each patient is evaluated with two approaches: genome-sequencing, using the Foundation One test, a tool developed by Foundation Medicine in Boston, USA, and a novel gene expression-based score co-developed specifically for this trial by collaborative efforts between Institute Gustav Roussy and us at Ben-Gurion University of the Negev, Israel. Each patient is reviewed by an expert panel, which decides if a Foundation One test has resulted in actionable recommendations. If yes, the patient is treated accordingly. If not, they turn to our expression-based report to choose a therapeutic approach. The goal is to treat 200 patients with this protocol, and to compare progression-free survival under the precision-recommended therapy to the last line of non-targeted therapy. Significant extension of progression-free survival patients would prove that PCM is helping to recommend more effective therapy.

Your lab is also investigating new methods to extract more information from expression profiles from whole biopsies. What prompted this research and how has it progressed to date?

On the one hand, I heard and read about the underappreciated role of the immune system in cancer. For example, ‘Immune evasion’ has recently made it into The Hallmarks of Cancer: the next generation – the latest in a series of seminal papers published by cancer researchers Douglas Hanahan and Robert Weinberg.

On the other hand, I was analysing data from The Cancer Genome Atlas, and it made me question: what about the immune signal? The biopsies used contain a small fraction of immune cells. What if we could enhance the signal they contribute to the published expression profiles? When I discussed this direction with immunologist Angel Porgador, he not only embraced the concept, but we ended up winning substantial funding to promote the idea. So far this approach has given us very exciting results, and we are still investigating the full implications of the signals that we have uncovered.
FOR DECADES, ADVANCES in information technology and its applications in biomedical research have transformed the understanding and treatment of a range of catastrophic and fatal diseases. Broadly termed bioinformatics, this field is culminating in the development of pioneering approaches to personalised or precision medicine, enabling specific therapeutics to be tailored for individual patients based on genetic and functional genomic information. While personalised treatments that improve efficacy and reduce loss of life are widely expected to form the basis of future medical paradigms for a range of diseases, the increasing amount of genetic, genomic, phenotypic and other ‘omics’ information now being captured and measured is not always translated into clinical care.

To fully utilise the data collected by medical institutes around the world, there is a pressing need to develop innovative resources capable of capturing, integrating and analysing a broad array of ‘omics and clinical information. At the forefront of efforts to meet the demand for more sophisticated and complex data processing tools, Dr Eitan Rubin and his team at the Medical Systems Biology laboratory at Ben-Gurion University of the Negev, Israel, have already taken huge strides, and their work could ultimately revolutionise the design and delivery of medicines for a plethora of diseases.

THE BASICS OF PCM
One area Rubin is committed to improving is the decision making behind precision cancer medicine (PCM), which is built upon the idea of comparing the properties of a tumour and prior knowledge relating to the efficacy of certain drugs. Because each cancer is unique, selecting appropriate courses of medical treatment for tumours is a major challenge, and researchers across the globe are striving to find associations between molecular states and specific medicines to identify potentially successful drugs for each individual patient they treat.

Given that the success of PCM development depends on the accessibility of prior knowledge and ability to utilise this knowledge effectively, the fact that the majority of existing information linking cancer drugs to potential biomarkers is disjointed and disorganised is a huge obstacle. In response, Rubin is working on several projects to harvest existing data about drug response-related markers, creating a new space that draws together this knowledge and makes it available to all, as well as on methods of translating it into new therapeutic and research tools.

A DYNAMIC COMMUNITY KNOWLEDGEBASE
Faced with a global dearth of usable drug-biomarker information, Rubin is leading a research team to create the PCM Wiki and Knowledgebase – a bespoke, two-pronged approach to data collation consisting of a structured knowledgebase in the back-end and a user-friendly, intuitive data entry and dissemination interface at the front. Based around formal methods of representing knowledge (eg. gene ontologies), which enable data to be effectively mined, merged, searched and filtered, the tool is designed to be practical to use for informing clinical decisions.
INTELLIGENCE

THE MEDICAL SYSTEMS BIOLOGY LAB

OBJECTIVE
To improve precision cancer medicine by better organising the relevant data, developing novel tools to identify multidimensional predictors of treatment outcome, and improving the protocols for sharing and evaluating data about drug efficacy and prediction methods.

KEY COLLABORATORS
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EITAN RUBIN received his PhD from the Weizmann Institute of Science, Israel, before working at Harvard University, USA, among other institutions. He is currently a senior lecturer in the Shraga Segal Department of Microbiology, Immunology and Genetics at the Ben-Gurion University of the Negev. His group is looking for new ways to study phenotypic variation in humans and connect it with an underlying genetic basis. Most of the group’s efforts concentrate on cancer, with a special emphasis on precision medicine and drug response.

The information stored in the knowledgebase in a computerised form is transformed into a reader friendly, Wikipedia-like page. This format comes either in the form of cancer-wide or drug-wide reports (summarising data mined computationally from the literature) or as case reports (describing patient reports from the community). The technology also allows users to record and upload their own knowledge – or correct the information provided by others – via an intuitive interface. As in the very popular Wikipedia, user-generated alterations, additions and highlighted errors in the knowledgebase become visible in real-time to any other user, resulting in a dynamic, community-driven and open-access knowledgebase of integrated and consolidated data on genetic markers, therapeutic decision and treatment outcomes.

CLINICIAN-CENTRED APPROACHES
In creating the PCM Wiki and Knowledgebase, Rubin’s team and its collaborators are committed to the clinician-centred approach, as they believe this will encourage open lines of communication and maintain the accuracy of the information. To achieve this, they have enabled clinicians to both initiate case reports and manually summarise the textual component of each record. “We have a deep belief that clinicians read, interpret and process the textual components of patients’ health records records much better than computers will ever be able to,” Rubin explains. This utmost professional respect for practicing clinicians is what gives the researchers the hope they are capable of creating a tool whose clinical use could eventually become widespread.

Keeping this clinician-centred approach in mind, the team is also seeking to take the novel step of incorporating case reports completed by patients and their relatives into the database by making the forms user-friendly for non-experts, while enabling end users to make a distinction between clinician- and patient-contributed information.

DEVELOPING WINTHER
Alongside his work on the PCM Wiki and Knowledgebase, Rubin is also part of the WINTHER trial, a cutting-edge project coordinated by the Worldwide Innovative Networking Consortium in Personalized Cancer Medicine. The trial is testing two complementary methods for employing systems biology combinatorial biomarker approaches to improve the effectiveness of cancer medicines: one that is based on the detection of genetic alterations [eg. sequence and copy-number alterations], and one that is based on the detection of changes in gene activity levels [eg. expression profiles].

The main goal of the trial is to evaluate the benefit of two complementary methods for predicting the effectiveness of drugs in cancer patients. As a secondary goal, the project is aiming to instigate a profound change in the design of clinical trials. To do this, the researchers are studying both the tumour and a sample of normal matched tissue simultaneously. Finally, by-products of this project include a database, algorithms and a computational tool that enable the prediction of drug efficacy at the individual patient level, regardless of the type of cancer in question.

If successful in fine-tuning the use of existing drugs and new compounds in clinical trials via the matching of appropriate drugs to each individual patient, WINTHER will also reduce the use of expensive drugs on patients who will not benefit from them. Like the PCM Wiki and Knowledgebase, as a clinically validated industry tool, WINTHER will help medical professionals ensure a greater number of patients are receiving personalised, precise and rationally selected therapies.

INVESTIGATING THE IMMUNE SYSTEM
Another aspect of Rubin’s work centres on immune profiling of the cancer microenvironment with an aim of improving PCM. Recently, he and his colleague, immunologist Dr Angel Porgador, undertook a computational examination of immune expression levels in 5,000 tumours to see if they could find a correlation with cancer virulence. The results were astounding. “We can clearly show the immune response to the tumour, often with a marked effect on the patients’ survival,” Rubin shares. “We are opening up a completely new way to consider how therapies may affect the tumour’s ability to supress immune response, which in turn may dramatically improve survival.”

Rubin and Porgador still have many goals to achieve before they can make full use of this new approach, and they are currently gathering samples and applying for funding to advance this project. “With sufficient resources, I believe we can start clinical testing of a new assay that can improve the prediction of treatment efficacy in less than three years,” Rubin enthuses.

THE ROAD AHEAD
These three projects mesh into the full range of relevant issues upon which Rubin’s lab is tirelessly working. At the heart of all of its efforts is a desire to improve patient outcomes. “We are working to apply state-of-the-art machine learning tools for the prediction of patients’ survival,” he shares. “We are also developing the required infrastructure and guidelines for making future discussion of survival analysis with machine learning more informative.” Subsequently, there is a great deal of optimism among Rubin and his colleagues that through their concerted efforts more effective means of cancer treatment could soon become a reality.