Taking cancer out of the equation

Multi-skilled investigators Professor Vittorio Cristini, Assistant Professor Eugene Koay and Associate Professor Zhihui Wang describe their exciting new approach to cancer treatment, illuminating the positive impacts that a mathematical view of the disease might help deliver.

Could you outline your long-term research objectives?

Our long-term goal is to establish a translational cancer modelling method that combines mathematical, engineering, experimental research and clinical data. This method is aimed at optimising treatment strategies for individual patients, especially in the context of highly malignant cancers. We have taken a multidisciplinary approach in our projects, which has resulted in novel mathematical modelling algorithms and insights into how and why cancer behaves the way it does in each patient. This new understanding is leading to original ways of thinking about the individual patient and design of rational treatment strategies that differ from individual to individual. Our ultimate goal is to bring our models to the clinic so that patient outcomes can be improved.

Why have you chosen to dedicate your work to the prediction and optimisation of treatment planning for patients?

Cancer still remains a major cause of death globally, and we thought it might be necessary to look at this disease from different angles. We started treating tumours as physical entities, or a combination of physical and biological problems, instead of focusing exclusively on the biological aspect. The fundamental rationale for this approach is that physical processes such as transport mechanisms for drug molecules within tissue and the forces exchanged by cancer cells with the surrounding tissue determine cancer growth and treatment outcome. By developing mathematical models to first reproduce and then predict tumour response to therapies, we are recasting this biological problem as a bio-engineering one. Hence, physicians on the forefront of treating cancer patients will have a quantitative tool to assist them instead of subjective assessments.

What skills and experiences do your collaborators bring to the table? Do you work in partnership internationally as well as nationally?

Each collaborator brings unique expertise to the table. We work with clinicians like Drs Jason Fleming and Steven Curley to keep our ideas closely connected to the forefront of clinical medicine. We work with leading research scientists such as Drs Anirban Maitra, Jeffrey Rosen, Michael Lewis, John Lowengrub, Sanjiv Gambhir, Jeff Brinker and Renata Pasqualini to connect our models to the underlying biological and physical mechanisms that drive cancers. This allows us to test whether our models are realistic and can help our collaborators gain new insights into the connections between physics and biology. We ultimately try to connect the biological and physical mechanisms with patient outcomes by working with all of these scientists. We currently focus on our research primarily in the US to further our proof-of-concept studies, but we do collaborate with scientists and clinicians from other countries as well.

Are any of these models being clinically translated? If so, what benefits can be expected?

Yes, a first-of-its-kind effort towards the development of prospective (and retrospective) clinical trials based on our published mathematical models of physical transport in tumours (Pascal et al., PNAS 2013; Pascal et al., ACS Nano 2013; Koay et al., JCI 2014) is underway, primarily at the University of Texas MD Anderson Cancer Center. The main purpose

Cell division

Cancer researchers at the University of Texas in Houston, USA, have succeeded in developing a range of highly promising predictive mathematical models of tumour progression and treatment outcome that could soon be aiding clinicians in the fight against the disease.
of these clinical trials is to elucidate the role of the physical properties of tumours in overall resistance to cancer drugs and patient outcomes. Our future research will continue to develop predictive models and analytic methods to facilitate clinical translation of these models.

It can be expected that this model-driven effort will help oncologists determine more effective, patient-specific drug treatment strategies, individualising the amount, frequency and delivery platform of drugs, and assessing the need for ancillary non-drug-based treatments.

**What is your research trajectory for the coming year?**

We are testing whether our growth model can be used to gain insight into the interactions between pancreatic cancer cells and the stromal cells around them. The stroma is composed of immune cells, fibroblasts and other cell types. Until recently, this stroma was thought to promote cancer cell growth and metastasis. New evidence suggests the stroma actually restricts aggressive cancer cell behaviour, and we believe our physical transport models can help explain why this may be the case.

The models will also be applied to emerging treatment modalities such as metabolic therapy and immunotherapy. These promising treatments can also be described by physical processes, and our approach may provide insight into why some patients do not respond to them.

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**THE PREDICTION PROBLEM**

One prominent affliction known for its variability and unpredictability is cancer. Chemotherapy remains the weapon of choice for defeating most forms of the disease – but as many people who have known patients suffering with cancer will be aware, it is difficult even for clinicians to predict with accuracy the outcome of such therapies. Although more advanced treatments like molecularly targeted therapy, metabolic therapy and immunotherapy can offer promising results, they too are unpredictable – especially since the qualities of a tumour can vary so dramatically between patients, and are dependent on the tissues from which it arises. Successfully modelling tumour growth and treatment response, therefore, would seem an almost impossible challenge.

Incredibly, one group of researchers based in Texas is on the verge of accomplishing just this. Professor Vittoria Cristini and Associate Professor Zhihui Wang both work at the Department of Nanomedicine and Biomedical Engineering at the University of Texas Health Science Center at Houston. Alongside physician scientist Assistant Professor Eugene Koay from the University of Texas MD Anderson Cancer Center’s Department of Radiation Oncology, and with the help of an interdisciplinary network of colleagues from across the nation, the scientists have published promising results towards a predictive model of cancer progression and therapeutic outcome.

**GROWTH AND TREATMENT**

Broadly speaking, there are two important types of models that Cristini, Wang and Koay have developed. The first group includes models of cancer treatment response, which enable the researchers to gauge from the physical properties of the tumour what its reaction to certain therapies is likely to be. These models work by creating an accurate simulation of drug delivery and assessing its effectiveness by examining the volume of the tumour occupied by blood vessels, the typical size of the blood vessels and the average distance separating them. By taking each of these three factors into account, the models can predict how much of a tumour will be reached and killed by the treatment, allowing clinicians to personalise courses of therapy before they even begin.

The second set of models describes the predicted growth of solid tumours, giving an insight into the presentation of such growths and possible routes towards curbing their expansion. Glioblastoma, pancreatic cancer and breast cancer are all lethal diseases with their own particular patterns of progression; but they share mechanisms that determine their proliferation – intercellular interactions and fluctuating supplies of oxygen and glucose.
TRANSLATIONAL RESEARCH: MATHEMATICAL MODELLING OF CANCER TREATMENT

OBJECTIVE
To develop a translational cancer modelling approach that combines mathematical, engineering, experimental research and clinical data to improve treatment strategies.

KEY COLLABORATORS
Dr Jason Fleming, Dr Anirban Maitra, University of Texas MD Anderson Cancer Center, USA • Dr Steven Curley, Dr Michael Lewis, Dr Jeffrey Rosen, Baylor College of Medicine, USA • Dr Jeffrey Brinker, Dr Renata Passqualini, University of New Mexico, USA • Dr John Lowengrub, University of California, Irvine, USA • Dr Sanjiv Sam Gambhir, Stanford University, USA

PARTNERS
University of Texas Health Science Center, USA • University of Texas MD Anderson Cancer Center, USA • University of New Mexico, USA • University of California, USA • Baylor College of Medicine, USA • Stanford University, USA • Massachusetts General Hospital, USA • King Abdulaziz University, Saudi Arabia

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CONTACT
Professor Vittorio Cristini
T +1 505 934 1811; +1 713 686 5627
E vsacristini@gmail.com; vittorio.cristini@uth.tmc.edu

VITTORIO CRISTINI is a distinguished professor and the Vice Chairman of the Department of Nanomedicine and Biomedical Engineering at the University of Texas Health Science Center at Houston. He has authored over 80 publications in peer-reviewed scholarly journals and a book monograph entitled Multiscale modeling of cancer: an integrated experimental and mathematical approach, published by Cambridge University Press in 2010. Cristini was named one of 99 ISI Highly-Cited Researchers in Mathematics, and one of the world’s most influential scientific minds by Thomson Reuters.

EUGENE KOAY is an assistant professor in the Department of Radiation Oncology at the University of Texas MD Anderson Cancer Center. He is a physicist scientist who studies how the physical properties of cancer influence its biological behaviour and response to therapy. This approach has led to novel methods of analysing the diagnostic imaging and pathology of patients with pancreatic and hepatobiliary cancers.

ZHIXIANG WANG is an associate professor in the Department of Nanomedicine and Biomedical Engineering at the University of Texas Health Science Center at Houston. His research primarily focuses on hybrid multiscale modelling, biophysical modelling and cross-scale drug target discovery. Wang completed a postdoctoral fellowship at Harvard Medical School and Massachusetts General Hospital in 2010.

Fitting the model to patient data. Symbols: measurements from 49 histology images of CRC metastatic to liver in the first cohort of patients, with SDs (six measurements per tumour nodule). Dashed line, quadratic least-square fit; red line, least-square fit of the model to the data (coefficient of determination $R^2 = 0.92$; $R^2 = 0.94$ between the two curves). [Inset] Parameter values obtained from fit. Reproduced from Pascal et al., PNAS 2013.

for example. Although different cancers behave differently, Cristini emphasises that he and his colleagues are not narrow-minded in their studies: “We are not currently focusing on any particular type of cancer, as the underlying physics is universal. We fine tune the model parameter values and revise model assumptions for each specific cancer type.”

THE THREE-STEP PROCESS
In 2013, the group published a paper [Pascal et al., PNAS 2013] demonstrating the efficacy of its treatment model in predicting the responses of glioblastoma and metastatic colorectal cancer to certain drugs. Validating their models in this way is the second stage of a three-step process for Cristini and his colleagues; first, they develop the models, a time-consuming challenge that involves translating biophysical tumour properties and the diffusive and perfusive behaviour of drugs in tissue into ordinary and partial differential equations. As part of this process, the cellular uptake of drug molecules is also considered [Pascal et al., ACS Nano 2013], as well as the spatial domain represented by the tumour and surrounding tissues. Importantly, in order that the models can be serviceable for clinicians and patients down the line, the researchers base their models on parameters that would be readily available from computed tomography and magnetic resonance imaging scans, tissue analyses, mammograms and other minimally invasive procedures that many patients will already have undergone.

As was the case in the 2013 paper, the model is then validated against multiple cancer types and datasets. If this validation process is successful, then the investigators can move to the final stage of the process – examining prospective applications in the clinic, and using the model to predict patient outcomes. When either of the first two steps produces unsatisfactory results, however, they are forced to return to the drawing board, honing their model to bring it in line with the progression of tumours as observed.

BENCH TO BEDSIDE
Going forward, Cristini, Wang and Koay will be making the most of their collaborative network, which extends across research and clinical science, to bring their tool into the hands of practitioners. Having successfully completed the first two stages of their three-step process, clinical trials have now begun to test the models both against the progress of current patients and against details collected on previous patients to ascertain their accuracy both retroactively and in practice.

There will be significant translational value in this work as soon as the trials are complete, but the future may bring further benefits as well. Cristini anticipates that the approaches he and his colleagues have developed will be useful in contexts beyond cancer, in relation to drug delivery more generally, regenerative medicine and even tissue engineering. Modelling biological systems mathematically may not sound like a common research interest, but the achievements of the group demonstrate that even a disease as unpredictable as cancer is not beyond the reach of numerical logic.