kinase inhibitors have shown relatively modest activity as single agents. It is anticipated that clinical development of these agents will involve first combining them with cytotoxic agents and subsequently with other signaling inhibitors. However, the number of potential combinations of signaling inhibitors is daunting, and there is a lack of knowledge about human cancers that may be used to guide the use of individual targeted agents or for the rational choice of combinations. Further, inhibiting one pathway can lead to upregulation of other pathways as part of the cellular stress response. Understanding which pathways are critical for cancer cell proliferation and survival under physiological and stress conditions will be critical in understanding how best to combine agents.
Dysregulation of the phosphatidylinositol 3 kinase (PI3K)-Akt-mTOR pathway occurs frequently in human cancer. Oncogenes, overexpressed receptor tyrosine kinases and constitutively activated mutant receptors, amplification of the p110 catalytic subunit of PI3K, loss of PTEN phosphatase function, amplification of Akt2, inactivating mutations of the tuberous sclerosis proteins hamartin and tuberin (TSC1/2), and overexpression the small G-protein Rheb (in transformed cells) activate mTOR (mammalian target of rapamycin) a serine/threonine kinase that through control of translation initiation, regulates cell size, proliferation, survival and responses to cellular stress (nutritional deprivation, cellular energy charge and hypoxia). Overexpression or amplification of eIF4E (the RNA cap-binding protein) downstream of mTOR in many human cancers also indicates the role of this pathway in maintenance of the transformed phenotype. Here we will explore the role of preclinical models in identifying combinations of targeted agents building on mTOR inhibition. Examples to be considered are the combination of inhibitors in different signaling pathways that impinge on a common product, and combinations of inhibitors of different steps within the same signaling cascade that may circumvent stress-induced pathways.

## Wednesday 29 September 10:15–12:00

**WORKSHOP 4**

# Practical issues in tissue research

**18** INVITED

### US NCI perspective on tissue handling and banking

S.E. Taube. *National Cancer Institute, NIH, Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis, Rockville, MD, USA*

The National Cancer Institute (NCI) of the US has long supported the collection and distribution of human specimens to facilitate research. Different models have been developed to meet varying research needs. These have included procurement, traditional tissue banks and virtual tissue banks. The procurement model enables researchers to identify the types of specimens they require and the format they prefer; the resource staff coordinate with participating hospitals to acquire the necessary surgical specimens. Traditional banks are centralized repositories where specimens are submitted and held until requested. The virtual bank model the NCI has used involves centralizing the data associated with specimens, but leaving the specimens at the sites where they are archived until they are requested. The data associated with the specimens varies with the purpose of the collections and the needs of the research. Procedures have been developed for both pathology review and data quality assurance. Informed consent and other regulatory issues have also been addressed and modified as new regulations have been put in place. Rules for accessing specimens differ depending on how limited the availability of specimens is and the nature of the associated data. The various models will be presented with discussion of how well they are meeting research needs and what gaps remain. Challenges will be described as well as innovative plans to address anticipated needs.

**19** INVITED

### US Cooperative Group perspective on tissue handling and banking

R. Schilsky. *University of Chicago, Pritzker School of Medicine, MC 1000 Biological Sciences Division, Chicago, USA*

Conducting correlative science studies requires a coordinated system that includes centralized and standardized collection of patient specimens; storage under controlled conditions with appropriate safeguards; pathology quality control; a comprehensive inventory; a process to distribute specimens to approved investigators consistent with patient consent and to receive the research results from investigator laboratories; and policies to safeguard patient confidentiality. Ultimately, the results of the laboratory studies must be linked to and correlated with the clinical outcomes of patients treated on clinical trials. The US cooperative group program includes 9 NCI-funded groups that conduct multi-center studies of cancer prevention, treatment, biology and health outcomes. Each group operates one or more repositories that collect a variety of human specimens including frozen tumor tissue, paraffin-embedded tumor and normal tissue, germline DNA and serum. These specimens are collected from patients enrolled on clinical trials and are accompanied by detailed information on patient characteristics, treatment and outcomes. CALGB protocols contain instructions for specimen acquisition, handling and shipping and CALGB uses customized specimen tracking software to monitor sample shipping, receipt and distribution. Standardized procedures for specimen storage and distribution are in place at all CALGB repositories each of which is designed according to the guardian repository model. Investigators are asked to provide local IRB approval of research studies and to sign an investigator agreement before receiving specimens from a CALGB bank. Despite these well-established procedures, many barriers remain to correlative science research in the cooperative group program. These include variability in local IRB review/approval for such studies; variability in specimen handling across multiple sites and at multiple repositories with varying expertise/resources; lack of uniform policies and procedures for access to and use of human specimens; lack of harmonization of guidelines across the multiple federal and state agencies that oversee such research and lack of standard approaches to specimen/data ownership and intellectual property. The cooperative groups have begun to address these issues collaboratively with NCI through formation of the Group Banking Committee that will establish uniform minimum standards for specimen handling/banking across the cooperative group program.

**20** INVITED

### Current challenges of national and pan European human tumour banking

M.M. Morente. *Spanish National Cancer Center – CNIO, Spanish National Tumour Bank Network, Madrid, Spain*

Current oncological research has three main characteristics: The capacity for large-scale studies in genomics and proteomics, the high sensitivity of the current tools, and the transfer from basic to clinical research. All these three characteristics are dependent of especially procured tissues: Large-scale molecular studies need large numbers of cases to identify new parameters of clinical value, highly sensitive techniques require appropriately handled samples, and the translational research needs homogeneous tissue-sampling protocols avoiding the bias of multicentre studies.
Some of the more urgent challenges in Tumour Banking include:
A new hospital strategy
Tumour Banking requires collection, freezing and storage of neoplastic and normal tissues and these activities must be considered a routine in the Departments of Pathology although they must be considered from the hospital point of view including new type of Biorepositories in parallel such as: Serum banks, minimally passaged tumour cell lines for drug checking and, mainly, clinical data.
Networking
As previously mentioned, current oncological research needs of a large number of cases homogeneously treated, followed up and with tissue samples in the context of multicentre and multinational projects. For this reason, networking appears the best environment where TB must grow. Spanish, UK or EORTC networks can be taken like a model in this issue
Integration in clinical trials and projects of excellence
The best role to be play for TB in Translacional research is its close integration of Tumour Banks in clinical trials of excellence including molecular profiling by using frozen samples with protocolised clinical information.
Ethics and laws
Although there are broad principles regarding the use of human tissue material in Europe and the US, the various laws and customs in the different countries or States show that national laws and custom still dominate. Occasionally, there are conflicts in the laws and policies between these nations and states. To solve this diverse legislations is, perhaps, the most important challenge for Tumour Bank Networking in the very close future. Europe needs a common legislation which explicitly would cover the use for research, not only for clinical practice or genetic susceptibility studies, of surplus diseased and normal tissue, linked histopathological data and relevant clinical information, with a linked-anonimased design. This common legislation o directives, independently to what has presently been legislated by others, could start forming a common legislative body for European countries, so that it enables and enhances the development of international multicentre studies.