

Gastrointestinal Cancer *Clinical Research Unit*



Manuel Hidalgo

Clinical Research Unit Head

Manuel Hidalgo was born in Antequera, Malaga, in 1968. He received his MD from the *Universidad de Navarra*, Pamplona, in 1992 and his PhD from the *Universidad Autónoma de Madrid* in 1997.

Manuel specialised in Medical Oncology at the *Hospital Universitario 12 de Octubre*, Madrid, obtaining his license in 1996. He completed his training in drug development at the University of Texas Health Science Center, San Antonio (USA), where he briefly joined as Faculty. He then moved to Johns Hopkins University in 2001 as Co-Director of the Drug Development and GI Programmes.

He joined the CNIO in 2009 to lead the GI Cancer Clinical Research Unit. Manuel is a founding member of the pancreatic cancer research team – a clinical trials group focusing on novel therapeutics for pancreatic cancer. He has participated in the clinical development of more than 30 novel anticancer agents and led the early clinical trials with erlotinib and temsirolimus – two recently approved drugs.

Manuel's work has contributed to the incorporation of molecular endpoints in early clinical trials. His group pioneered the utilisation of personalised xenograft models for drug screening, biomarker development and personalised cancer treatment.

He has published 170 papers in peer-reviewed journals and his work has been funded by the NCI, AACR, and ASCO.

Manuel received an AACR Clinical Research Fellowship and an ASCO Career Development Award for his work on the development of EGFR inhibitors. His most recent efforts focus on novel therapeutics for pancreatic cancer.

Summary

The GI Cancer Clinical Research Unit focuses on novel therapeutics for patients with cancers of the alimentary tract. Our research includes developing personalised xenograft models for drug screening and biomarker development, carrying out innovative clinical trials and personalised patient treatment.

In pancreatic cancer our most recent work has focused on therapeutically exploiting the data obtained from analysis of the pancreatic cancer genome; development of strategies to target the pancreatic cancer stroma; approaches to eliminate pancreatic cancer stem cells as well as novel strategies for personalised medicine.

Strategic Goals

- Screen for novel drugs and drug combinations in personalised xenograft models of pancreatic and colon cancer
- Understand the mechanism of action and full spectrum of activity of nab-paclitaxel in pancreatic cancer
- Determine the effects of targeting EGFR in *KRAS* mutant pancreatic cancer
- Implement a protocol for personalised treatment of patients with pancreatic and colon cancer
- Initiate early clinical trials with novel agents in patients with these diseases



Staff scientists: Pedro P. López and Pia Morelli. **Post-doctoral fellows:** Antonio Calles (since February) and Mónica A. Musteanu (since October). **Graduate student:** Raquel Martínez. **Technicians:** Manuel Muñoz and Raquel Rey.

Highlights

During 2010 we have continued the lines of work initiated in 2009. Most of the current activities are at the preclinical level but we anticipate clinical trials to start over the next academic year – both with investigational new agents as well

as personalised medicine strategies. This year, we were also commissioned to write the Medical Progress in Pancreatic Cancer for the *New England Journal of Medicine* which summarises the current panorama of this disease (Figure 1).

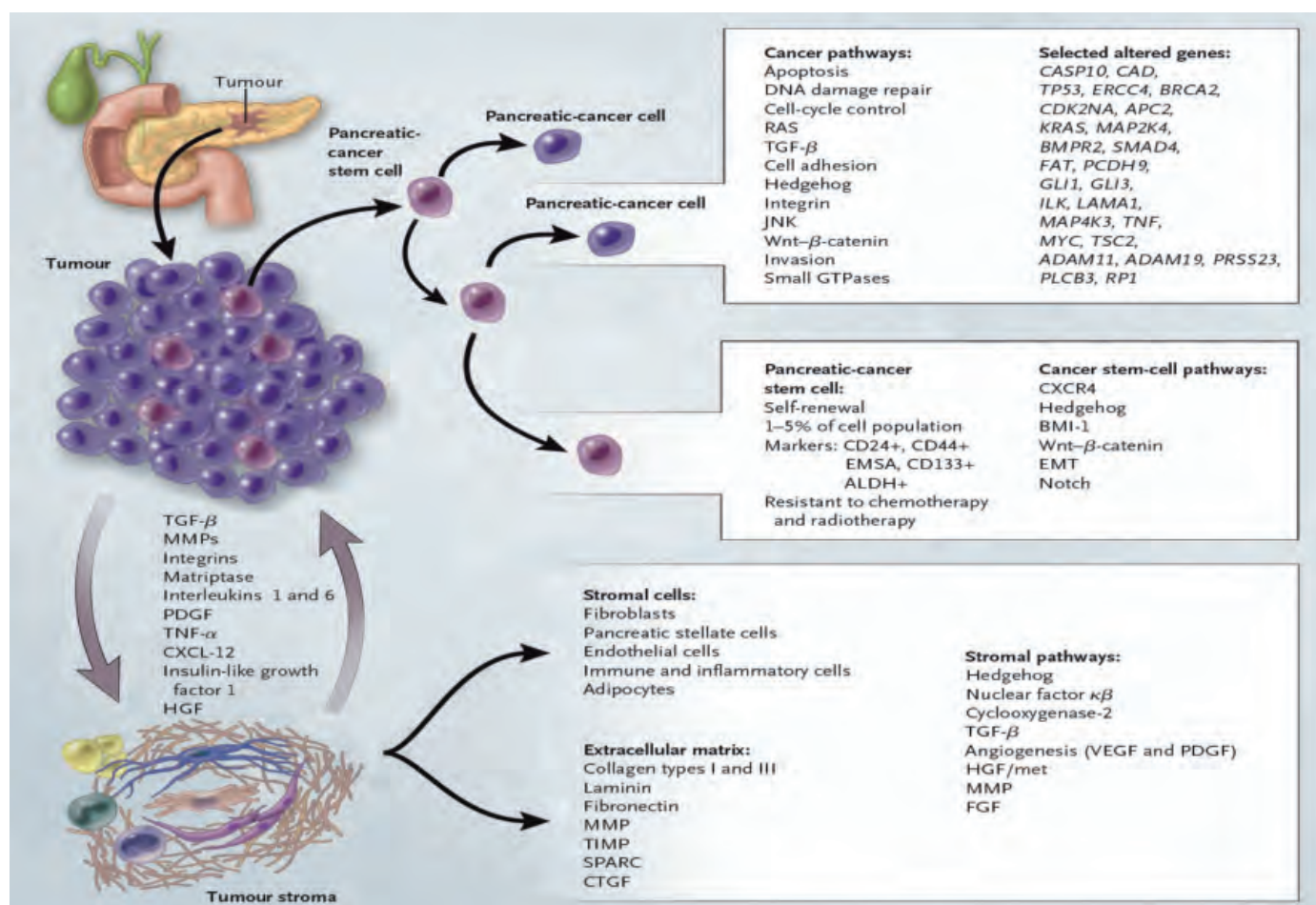


Figure 1: Multifaceted Biology of Pancreatic Cancer. Pancreatic cancer is composed of at least three compartments with unique biological properties: genomic alterations in pancreatic cancer cells; inherent properties of cancer stem cells; and lastly, the importance of the pancreatic cancer stroma in relation to treatment implications.

Novel therapeutics for pancreatic cancer

We have continued with research initiated at Johns Hopkins – the search for new agents against pancreatic cancer in our preclinical models. We have completed a prospective generation and molecular characterisation of pancreatic cancer xenografts and have submitted this work for publication. Our most recently published work on the screening of novel therapeutics against pancreatic cancer has focused on mTOR inhibitors. Complete, yet to be published studies involve Wee, CDK inhibitors, an oral formulation of gemcitabine, and IGF1R. We are currently also investigating the targets PARP, PI3K and PI3K-mTOR, hedgehog, and tubulin.

In addition to testing new drugs with exciting mechanisms of action through

collaboration with the industry, we are planning to soon start testing CNIO's proprietary agents in collaboration with the CNIO Experimental Therapeutics Programme. We are also interested in compounds that target pancreatic cancer stem cells (CSC) and envisage continued collaboration with the CNIO Stem Cells and Cancer Research Group led by Christopher Heeschen, exploring agents against this cellular compartment.

Our most recent studies demonstrate that personalised xenografts retain cancer stem cells and that this could be an interesting model to test anti-CSC therapeutics. We participated in a study (our first collaborative CNIO project) which showed that the triple combination of gemcitabine, rapamycin and a hedgehog inhibitor leads to substantial elimination of pancreatic

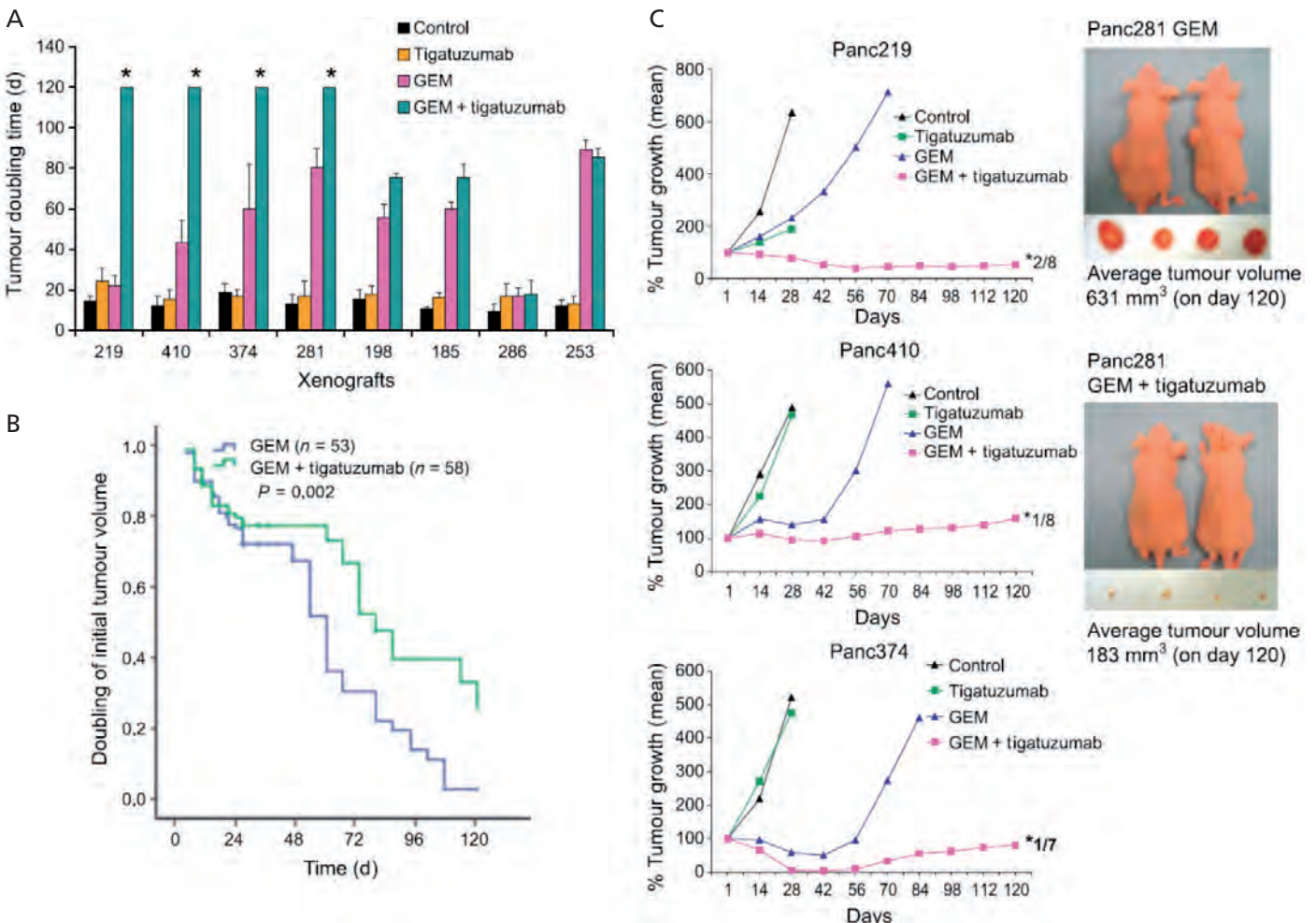


Figure 2: Targeting the DR5 Receptor in Pancreatic Cancer. (A) Tumour doubling time of PDA xenografts treated with gemcitabine, the DR5 agonist CS-1008 and the combination, followed without treatment. (B) Kaplan-Meier curve showing significant delay in tumour growth in cases treated with gemcitabine and CS-1008. (C) Representative growth curves from individual tumours.

cancer stem cells and prolongs tumour control in mouse models of pancreatic cancer. We also obtained similar results targeting the DR5 receptor, which have been recently published (Figure 2). For 2011 we plan to start the first Stand Up to Cancer (SU2C) sponsored clinical trial.

Finally, it is becoming clear that the stroma plays an important role in pancreatic cancer. We have found that our freshly generated pancreatic cancer xenograft model nicely recapitulates this characteristic of human pancreatic cancer. This is in contrast to conventional cell lines in which the stroma is completely lost when xenotransplanted into nude mice. We have observed that nab-paclitaxel – a nanotechnology formulation of paclitaxel currently in phase III clinical trials with quite promising early clinical data – may indeed work by targeting the pancreatic cancer stroma. We have now shown that SPARC is definitely expressed in early precursors of pancreatic cancer and are currently carrying out additional preclinical studies to optimise and exploit this target therapeutically. We have also initiated a clinical trial to demonstrate this concept in the clinical setting.

Personalised treatment of pancreatic cancer

Over the last few years we have conducted different systems biology analysis in 30 pancreatic cancer xenografts, for which we have complete clinical data as well as live xenografts. We found that *PALB2* was one of the mutated genes in this screen. We also showed in a recently accepted paper that the tumour responded to mitomycin C treatment, both in preclinical and clinical studies. Our most recent data demonstrates that this tumour is also sensitive to PARP inhibitors representing a new line of treatment for this patient in the future.

We have developed a new method of personalised medicine using our growing database of well-characterised individual patient tumours which includes both extensive genomic information as well as treatment response increases. The initial results from this effort have been communicated in a manuscript. Our approach is based on matching tumours to a reference database and extrapolating drug responses. We are currently initiating a clinical trial sponsored by the SU2C programme to test this approach in pancreatic cancer patients.

Publications

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