



WELCOME TO THE WINTER 2015 NEWSLETTER FOR THE EU PROJECT ANGIOPREDICT

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The Angiopredict team at the Leuven plenary meeting on 13 November 2014.

FOR FURTHER INFORMATION ABOUT ANGIOPREDICT PLEASE SEE THE PROJECT WEBSITE [HTTPS://WWW.ANGIOPREDICT.COM](https://www.angiopredict.com)



ANGIOPREDICT IN SHORT – OUR KEY AIMS AND OBJECTIVES

Colorectal cancer is the second most common cause of cancer-related deaths in the developed world. Currently, the first line treatment for patients with mutations in Ras/Raf/ PI3K pathways who do not respond to anti-EGFR treatment is bevacizumab (bvz, Avastin®) in combination with chemotherapy. However, the treatment is not effective in all patients - which may result in some patients suffering related side effects, without benefit.

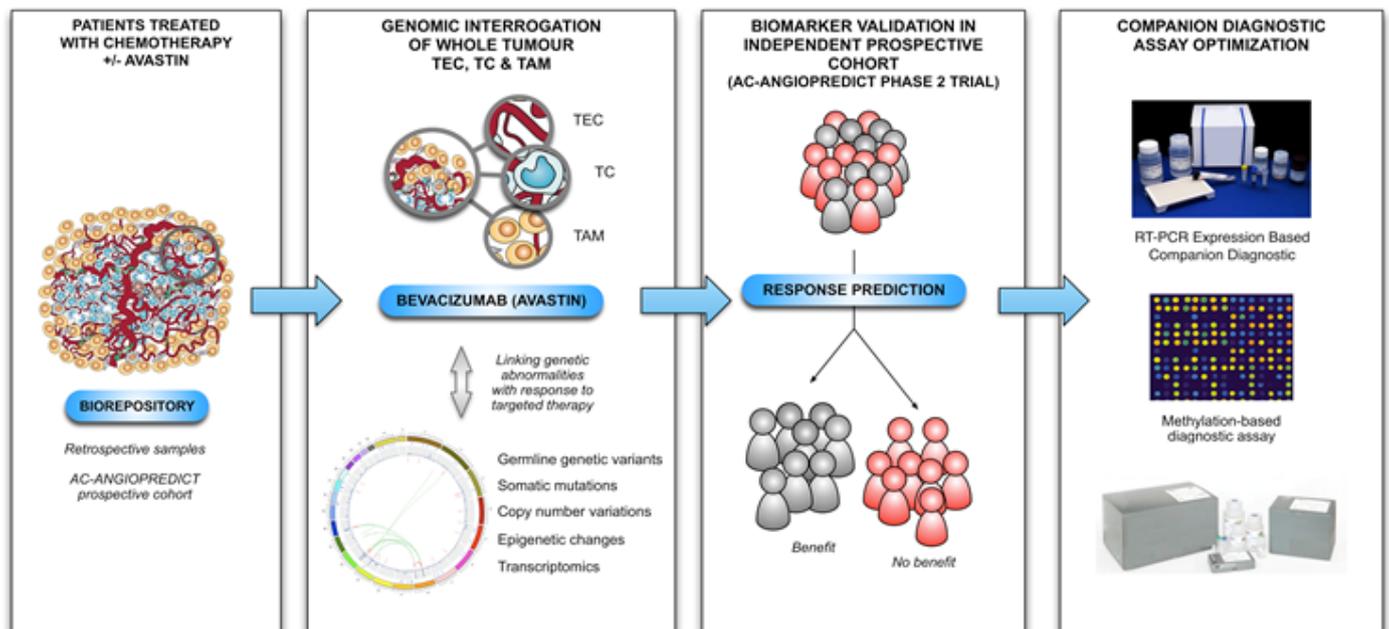
In ANGIOPREDICT, academic cancer biologists and industry-based biotechnology researchers are working together with clinicians to identify biomarkers to predict whether individual metastatic colorectal cancer patients will respond positively to Avastin® combination therapy. Diagnostic tests using these biomarkers will be developed in the project to provide clinicians with the means to predict patient treatment responses in the future. Our ultimate objective is to help guide clinical decision-making in mCRC (ensuring the right treatment is selected for the right patient at the right time) and to facilitate delivery of more focused and cost-effective care.

Our ultimate objective is to help guide clinical decision-making in mCRC, ensuring the right treatment is selected for the right patient at the right time

The overall approach is as follows:

- ANGIOPREDICT partners are analysing existing tissue samples from patients receiving Avastin® combination therapy or chemotherapy, to identify potential predictive biomarkers.
- The predictive ability of these potential biomarkers will be validated using other tissue samples (e.g. from the AC-ANGIOPREDICT clinical trial), where patients are receiving Avastin® combination therapy.
- Validated, predictive biomarkers will then be used to develop diagnostic tests that can be used by clinicians to identify which patients will benefit from Avastin® combination therapy.

The graphic below illustrates the Project workflow.



READ ALL ABOUT IT

AN UPDATE ON ANGIOPREDICT PUBLICATIONS

Although ANGIOPREDICT runs until 31 January 2016, we have already achieved some key publications related to the work of the Project. Some of the most significant publications to date are described below.

“Genetic markers of bevacizumab-induced hypertension”, (Lambrechts et al., *Angiogenesis* 17:3:685).

This article addresses whether genetic variation in vascular endothelial growth factor-A (VEGF-A) pathway or hypertension-related genes are associated with bevacizumab-induced hypertension.

“DNA copy number analysis of fresh and formalin-fixed specimens by shallow whole-genome sequencing with identification and exclusion of problematic regions in the genome assembly” (Sheinin et al., *Genome Research advance on-line* 15/9/2014).

Detection of DNA copy number aberrations by shallow whole-genome sequencing (WGS) faces many challenges. This article presents a robust, cost-effective WGS method for DNA copy number analysis that addresses many of the most significant challenges faced by currently available procedures. For most samples the new sequencing and analysis processes yield genome profiles with noise levels near the statistical limit imposed by read counting. The described procedures also provide better correction of artifacts introduced by low DNA quality than prior approaches and better copy number data than high-resolution microarrays, at a substantially lower cost.

“Biomarker-driven Studies in Metastatic Colorectal Cancer (mCRC): Challenges and Opportunities” (Van Cutsem, Eric et al., *The Journal of OncoPathology*, Volume 2, Number 4, November 2014, pp. 37-45(9.)).

This paper explores the search for molecular biomarkers that predict the likely response to targeted treatments for metastatic colorectal cancer (mCRC).

A number of promising biomarkers of response to anti-angiogenic agents and the multikinase inhibitor, regorafenib, are currently under investigation in ongoing studies, though inter- and intra-tumor heterogeneity and the dynamic process of tumor evolution during treatment present major challenges to biomarker research and drug development. The article concludes that overcoming these challenges requires the application of novel approaches to the assessment of biomarkers, innovative clinical trials that employ statistical approaches and the combined expertise of major research consortia using systems biology approaches to the identification and validation of predictive biomarkers in mCRC.

“Patient-Derived Xenograft Models: An Emerging Platform for Translational Cancer Research” (M. Hidalgo et al., *Cancer Discov*; 4(9); 1–16. ©2014 AACR).

Recently, there has been an increasing interest in the development and characterization of patient-derived tumor xenograft (PDX) models for cancer research. These models are useful for drug screening, biomarker development, and the preclinical evaluation of personalized medicine strategies. This article summarizes the current state of the art in this field, including methodologic issues, available collections, practical applications, challenges, shortcomings and future directions, and introduces a European consortium of PDX models.



Dr Annette Byrne, from the Royal College of Surgeons of Ireland (Coordinator of Angiopredict)



“Markers of response for the antiangiogenic agent bevacizumab.” (Lambrechts D. et al. J Clin Oncol. 2013 Mar 20;31(9):1219-30).

This article discusses progress towards finding robust

biomarkers that can guide selection of mCRC patients for whom bevacizumab therapy is most beneficial. The current challenge identified is to expand the set of candidate markers emanating from recent studies and to validate and implement them into clinical practice.

LATEST NEWS

RECENT DEVELOPMENTS AND EVENTS

Since the last newsletter, project partners have been involved in numerous dissemination activities, reaching a broad audience, from the scientific community to the general public. These dissemination activities include:

- Angiopredict partners participated in a key International Expert Summit on Metastatic Colorectal Cancer held in Berlin in July 2013. Angiopredict features in the report published by the Angiogenesis Foundation following the meeting, which looks at current barriers and challenges in treatment and the development of possible solutions.
- Angiopredict post-doctoral researchers Dr Alice O'Farrell and Dr Ian Miller recently hosted visits to the Royal College of Surgeons in Ireland (RCSI)



Dr Alice O'Farrell and 5th Year students from St Mary's School, Baldoyle, Dublin at the RCSI.

by local secondary school students. The presentations covered general information about research science, aspects of the Angiopredict project and an introduction to non-invasive imaging.

- On 26th February 2014 a lecture on cancer therapy was delivered free of charge to the public by Dr David Murray (Angiopredict Post-doctoral Researcher) at the Royal College of Surgeons in Ireland as part of the RCSI Minimed Open Lecture Series. The lecture was entitled 'Tackling Cancer by Targeting Tumour Blood Vessels'.
- Prof Jochen Prehn (RCSI) presented on "Application of systems biology models of apoptosis signalling in a clinical setting; towards novel patient stratification tools" at the Europe-Brazil Meeting on Systems and Synthetic Biology, in Natal, Brazil, on 10 March 2014.
- Project Coordinator Dr Annette Byrne (RCSI) and Scientific Coordinator Prof Diether Lambrechts (VIB) presented during the Genentech/Roche sponsored Angiogenesis Biomarkers session at the 5th International Meeting on Angiogenesis at Vrije University Medical Centre, Amsterdam on March 14th, 2014.
- On 13 May 2014 Prof Dr Bauke Ylstra (VU-VUMC) delivered an invited lecture at the International Society of Cellular Oncology, which focussed on copy number and quality assurance with next generation sequencing from FFPE material. Prof Ylstra also presented on this topic at the 4th International Sym-



posium on Translational Oncology (19, September 2014, Barretos, Brazil) and at the American Society of Cancer Research ASCR (San Diego, 8 April 2014).

- Project Coordinator Dr Annette Byrne and former Angiopredict PI Prof Heinrich Huber presented at the European Research Workshop in Digestive Oncology in Barcelona on 24 June 2014. The workshop focused on biomarker-driven studies in metastatic colorectal cancer (mCRC) and examined the challenges and opportunities offered by biomarker-driven studies.
- On 14 July 2014 Dr Ian Miller (RCSI) presented at the Annual Microbubble Symposium, Leeds, UK. Dr Miller's presentation was entitled "Assessment of Bevacizumab Mechanism of Action in mCRC In Vivo models Using Contrast



Angiopredict at The RCSI Minimed Open Lecture Series

- Enhanced Ultrasound Imaging".
- Bioinformatics code (called QDNAseq), was submitted by project partner VU-VUMC to BioConductor (open source, open development software project to provide tools for the analysis and comprehension of high-throughput genomic data) and a stable release version has been made publicly available.

WHAT'S NEXT?

In the coming months the project partners will be focusing on:

- Finalising results and completing project reports - as of January 2015 imminent reports relating to: SNP genotyping discovery, raw DNA sequence data, raw copy number alteration profiles, micro-array expression data, validated gene signatures and verification of transcriptomic profiling data.
- Following up on patients enrolled in the Angiopredict clinical trial (accrual has been closed on 28th February 2015).
- Collaborating e.g. next consortium meeting scheduled for June 2015 in Berlin.
- Compiling and analysing project results across work streams.
- Disseminating project results, including finalising publications and presenting at scientific events e.g. partners are scheduled to present at the AACR Tumor Angiogenesis and Vascular Normalization: Bench to Bedside to Biomarkers Meeting (5 - 8, March 2015, Florida, USA) and at the Anti-angiogenesis Biomarker Session at the Annual AACR Meeting 2015, (18 - 22, April 2015, Philadelphia, USA).
- Developing the project's exploitation plan for the management, exploitation and commercialisation of the innovations and intellectual property generated by the Project.



MEET THE ANGIOPREDICT TEAM

The multi-disciplinary consortium is composed of cancer researchers, biotechnology companies, an experienced clinical trials organisation and clinicians from across Europe, supported by an experienced project management team.



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