IGOR D'ANGELO, PhD
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## PROFILE

Protein engineer with 10+ years industrial experience in therapeutic antibody generation and engineering.

## PRIMARY SKILLS and EXPERIENCE

- Expert in antibody optimization (i.e. improvement of affinity, stability, tailored specificity) using *in silico* predictive mutagenesis, *in vitro* maturation or combination approach.
- Familiar with establishing AI workflows (incl. feature selection, descriptor analysis) useful for developability prediction (i.e. thermostability, viscosity) of therapeutic antibodies and scFv modules.
- Familiar with statistical algorithms for supervised ML (SVM, RF, ANN, NBC and KNN).
- Experienced in designing libraries for in vitro affinity maturation (i.e. Yeast, Phage Display and Mammalian Recombination Technologies - HuTARG).
- Hands on experience with cloning, mutagenesis, expression in bacterial and mammalian cell lines and purification.
- Experienced in analyzing data from biophysical and functional characterization: i.e. DLS, DSF, UPLC-SEC, RP-HPLC, LC-MS, Flow Cytometry (FACS), immunoassays and SPR. Also experienced in analysis of MLR data (mixed leukocyte reaction), PK/PD, antibody dependent cellular phagocytosis (ADCP) and antibody dependent cellular cytotoxicity (ADCC).
- Developed several bi-and multi-specific protein and antibody scaffolds, including ADCs, targeting autoimmunity, inflammation, cardio-metabolic disorders and oncology.
- Experienced in running MD simulations and subsequent trajectory analysis.
- Experienced in analyzing deep sequencing (NGS) datasets from antibody repertoires.
- Applied new therapeutic modalities to tailor scaffolds to specific biology.
- Multi-year industry experience supporting programs focused on modulating effector function for applications in autoimmune disease.
- Experienced team leader (3-7 scientists); successfully planned and completed several internal and external projects, must-wins within Amgen and, previously with Zymeworks, in partnership with Merck, Inc., Xoma, Eli-Lilly Inc, Celgene and GSK.
- Multi-year experience in managing resources and cross-functional collaborations with immunologists, computational chemists, preclinical, process development scientists both internally and at various CROs, CMOs and business partners (non-GMP, GMP and GLP).
- Experienced in critically assessing projects, developing efficient workflows, formulating new ideas and providing scientific direction to increase success.
- Authored several peer-reviewed publications and contributed to invention disclosures for patent applications. Invited speaker at international conferences.

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## EDUCATION

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|---|---|
| Ph.D. Biochemistry and Molecular Biology, University of Heidelberg | 2000 - 2004 |
| Ph.D. Computational and Structural Biology, EMBL | 2000 - 2004 |
| M.Sc. Biochemistry, University of Pavia (Italy) | 1995 – 2000 |

IGOR D'ANGELO, PhD

## RESEARCH EXPERIENCE

### Just – Evotec Biotherapeutics – Scientific Director
### Seattle, WA
Mar 2022 – present

- Team and department leader for the Protein and Antibody Engineering unit of Evotec.

### Genomics Inst. of the Novartis Research Foundation, Associate Director - Antibody Engineering
### San Diego, CA
Nov 2020 – Mar 2022

- Providing guidance in antibody engineering and successfully co-leading a project on one of our nephrology programs.
- Team lead (7 scientists, 2 PhDs). Successfully promoted one of our scientists.
- Acting director for structural and computational modeling in the Biologics and Biotherapeutics department.
- Main point of contact for library design and NGS based analysis of antibody repertoires (B-cell).

### Amgen Inc, Senior Scientist – Antibody Engineering and Molecular Design. Mar 2016 – Nov 2020
### Vancouver BC, Canada and Thousand Oaks, CA

- Led a team of three scientists and integrated antibody engineering with the pre-existing molecular biology function.

- In the span of less than two years and in collaboration with several teams across four sites, brought to successful completion several projects connected to relevant therapeutics, two of which designated must-win for the Company (i.e. enabled successful bio-optimization, toxicology studies and formulation development).

- Successfully engineered Hu/Rt cross-reactivity in a time-sensitive manner for one of our lead migraine therapeutic antibodies (AMG334), enabling tox studies required prior to FDA approval. This product is now marketed as Aimovig™.

- Currently leading engineering efforts to develop a therapeutic antibody specific for selected regions of the SARS-Cov2 virus entry protein (Spike) (collaboration with Adaptive Biotechnologies).

- Successfully generated bispecific antibody leads for a cardio-metabolic program using in-vitro cell-based repertoire generation (HuTARG technology) in a novel non-canonical IgG-Fab scaffold and optimized it to tailor target receptor geometry.

- Significantly improved the thermostability of the BiTE molecule (without impacting target binding) using structure-based computational design in combination with iterative in vitro testing.

- Utilized structure-based algorithms to successfully design ad-hoc linkers for new BiTE

fusions with increased functionality.

- Successfully improved the potency of a lead Ab (influencing insulin secretion) by combining in vitro repertoire generation with FACS/NGS screening.

- Designed several unilateral mutations in the IgG4 CH3 domain to enable system-independent generation of highly pure bispecific antibodies directly from hybridoma supernatants, resulting in a patent.

- Provided guidance to generate pools of stable scFvs and worked to improve the bioavailability of VH domains as modules for new therapeutics in an anti TNFα surrogate antibody for several autoimmunity and inflammation programs.

- Contributed to the development of a new molecule registration platform.

Zymeworks Inc, Senior Scientist Jan 2011 – Feb 2016
Vancouver BC, Canada

- Part of a team of 4 scientists, created and optimized several construct libraries to enable highly specific antibody heavy-light chain pairing using a combined iterative structural modeling / *in vitro* approach.

- Created two novel single-chain antibodies (scMab) scaffolds with dual specificity enabling early bispecific proof of concept studies (incl. binding, cell-killing, internalization, phosphorylation and xenografts).

- Led a team of 4 scientists to engineer Fc:FcRn and FcFcγR interactions to control half-life and fine tune effector function using an asymmetric modality approach.

- Actively engaged in process development to natively express and characterize several bi-specific antibody scaffolds with a diverse set of geometries targeting several oncogenic markers and selectively co-engaging T and NK cell receptors.

- Designed stable antibody heterodimers with high dual specificity and natural Fc-like biophysical properties (licensed to Merck, Inc.).

- Brought to successful completion five separate projects (in the span of two years) with partner Eli Lilly, Inc. and Merck, Inc. aimed at the development of several multi-target bispecific Ab targeting autoimmunity, inflammation and cancer and assessment of their efficacy via tailored assays (i.e. MLR, ADCC, ADCP).

- Designed several novel albumin-like scaffolds with mono- (HER2, EGFR) and dual specificity (CD3/CD19, HER2/HER3, PDL1/TIM3, PD1/PD-L1) and improved their stability. Further improved efficacy by payload conjugation (ADC) and optimization of DARs.

- Established workflows for analysis of large datasets from mutational and fragment libraries (using SPR and DSF).

- Determined the crystal structure of a novel heterodimeric format of Trastuzumab Fc, following *in silico* predictive mutagenesis and construct optimization.

**Zymeworks Inc, Scientist** July 2009 – Dec 2010
**Vancouver BC, Canada**

- Using newly generated structural data, molecular simulations and *in vitro* screening, engineered several antibody molecules with tailored Fc mediated effector function, including an FcγRIIb superbinder and full FcγR knockout, resulting in multiple licensing agreements with large pharmaceutical companies.

- Optimized formulation and led efficacy studies (ADCC/ADCP, internalization, phosphorylation and PK/PD) of lead Fc-engineered antibodies.

- Determined the crystal structure of lead engineered Fc molecules in their free state and in complex with different FcγR, elucidating the role of single mutations and uncovering unique asymmetry in binding to specific Fcγ receptors.

**Canadian Light Source Inc, Research Associate** May 2008 - June 2009
**Saskatoon SK, Canada**

- Collected X-ray data (single and multi-wavelength), determined the crystal structure and contributed to determining the structure-activity relationship of several protein molecules in the frame of internal research and industrial access programs.

**University of British Columbia, Postdoctoral Res. Fellow** September 2004 - April 2008
**Vancouver BC, Canada**
**Advisor: Prof. Natalie CJ Strynadka**

- Characterized (biochemically and functionally) several molecules controlling the permeability of the intestinal epithelium in the context of Celiac Disease and gained experience in mammalian cell expression, localization studies and ileal tissue permeability assays.
- Expressed, purified, crystallized and determined the crystal structure of five cholesterol catabolic enzymes from *Mycobacterium tuberculosis*. Subsequently elucidated their structure-activity relationship (SAR), resulting in three publications.
- Performed expression studies on components of the T6SS bacterial translocon.
- Presented at several international conferences and received external funding through competitive scholarships.
- Worked collaboratively across multiple departments to advance research projects
- Gained certification to operate MALDI-TOF and QTOF Mass Spectrometer.
- Funding obtained through MSFHR post-doctoral fellowship.

**Univ. of Heidelberg / EMBL, Graduate Student** September 2000 - August 2004
**Heidelberg, Germany**
**Advisors: Prof. Matti Saraste and Dr. Klaus Scheffzek**

- Discovered the existence of a new bipartite phospholipid-binding module in the neurofibromatosis type 1 protein (NF1).
- Employed tools such as crystallography, bioinformatics, antibody generation, cell-based assays, LC-MS, IHC, confocal microscopy, lipid binding and lipid-mediated cell-signaling and quantitative proteomics to characterize the molecule from healthy individuals and NF1 patients.
- Proposed a model of structure-function relationship and confirmed it by rational mutagenesis. This model is generally accepted and published in a book chapter.
- Collaborated extensively with multi-disciplinary research groups.
- Presented at several international conferences and received external funding through international level competitive scholarships (MDC and EMBO).

University of Pavia, MSc Student — November 1999 – September 2000
Pavia, Italy
Advisor: Prof. Menico Rizzi

- Thesis work: Determined the crystal structure and catalytic mechanism of bacterial and human nicotinamide mononucleotide adenylyltransferase.
- Thesis work: Biochemical and *in vitro* enzymatic characterization of specific inhibitors of viral, prokaryotic and eukaryotic DNA replication, specifically inhibitors of *Clostridium difficile* DNA poltmerase IIIC, human Adenosine Kinase (AK), and HSV1 and HSV2 Thymidine Kinase (TK).
- Received additional funding through a competitive university scholarship.

## SELECTED PUBLICATIONS & INVITED SPEAKER

Kielczewska A, **D'Angelo I**, Foltz I, Amador S, Wang T, Sudom A, Pigott C, Min X, and Rathanaswa P. Development of a high affinity and potency human therapeutic antibody by novel application of Recombination Signal Sequence (RSS)- Affinity Maturation. JBC, 2021 JBC/2021/018942 – Accepted

**D'Angelo I**, Sanches M, Lario P, Poon D, Wickman G, Ng G, and Dixit S - AlbuCORE™ - Structure-Guided Engineering and Design of a Multi-Valent Albumin Scaffold with superior drug delivery properties. Mabs. 2020 12:1

Smakaj E, Babrak L, Ye J, Ohlin M, Shugay M, Briney B, Tosoni D, Galli C, Grobelsek V, **D'Angelo I**, Olson B, Watson C, Reddy S, Greiff V, Truck J, Miho E. Benchmarking immunoinformatic tools for the analysis of antibody repertoire sequences. Bioinformatics. 2020 Mar 1; 36(6):1731-1739.
**Igor D'Angelo** et al. National Hematology Congress, Oct 8, 2019 - Rome Italy. Overview of the Amgen BiTE platform.

**Igor D'Angelo** *et al* - European Antibody Congress, Oct 15-17, 2019 – Basel, Switzerland. Chairman and presenter.

Igor D'Angelo *et al* - European Antibody Congress, Oct 29-31, 2018 – Basel, Switzerland. Engineering Hu/Rt cross-reactivity for AMG334 (anti CGRPR) to enable Rat toxicology studies (GLP-TOX) and improving bioavailability, solubility and half-life for process development.

Igor D'Angelo et al - World Bispecific Summit, Sep 18-20, 2018 – Boston, MA - Understanding the True Value of Combinations of In Silico and In Vitro Analytical Approaches for Bispecifics.

Kielczewska A, **D'Angelo I**, Garcia S, Wang T, Sudom A, Min X, Rathanaswami S, Pigott C, Foltz I. Discovery of highly potent biologics by non-hypothesis driven in vitro affinity maturation. Nat Biotech. *Submitted.*

Corper A, **D'Angelo I**, Ohrn A, Samiotakis A, Urosev D, Sanches M, Lario P, Aguirre-Hernandez R, Tom-Yew S, Spreter T, Dixit S. Efficient generation of bispecific Abs via light-heavy chain interface engineering (2019). Mabs. *Submitted.*

**D'Angelo I** and Miho E. Novel Immunotherapies: Bispecific Monoclonal Antibodies. Review. Progress in Hematology (Italian). Nr 1 - 2020.

Von Kreudenstein TS, Escobar-Carbrera E, Lario PI, **D'Angelo I**, Brault K, Kelly J, Durocher Y, Baardsnes J, Woods RJ, Xie MH, Girod PA, Suits MD, Boulanger MJ, Poon DK, Ng GY, Dixit SB. Improving biophysical properties of a bispecific antibody scaffold to aid developability: quality by molecular design. MAbs. 2013 Sep-Oct;5(5):646-54.

Ludwiczek ML, **D'Angelo I**, Yalloway GN, Brockerman JA, Okon M, Nielsen JE, Strynadka NC, Withers SG, McIntosh LP. Strategies for modulating the pH-dependent activity of a family 11 glycoside hydrolase. Biochemistry. 2013 May 7;52(18):3138-56.

Welti S, Kühn S, **D'Angelo I**, Brügger B, Kaufmann D, Scheffzek K. Structural and biochemical consequences of NF1 associated nontruncating mutations in the Sec14-PH module of neurofibromin. Hum Mutat. 2011 Feb;32(2):191-7.

Dresen C, Lin LY, **D'Angelo I**, Tocheva EI, Strynadka N, Eltis LD. A flavin-dependent monooxygenase from Mycobacterium tuberculosis involved in cholesterol catabolism. J Biol Chem. 2010 Jul 16;285(29):22264-75.

Malakhova M, **D'Angelo I**, Kim HG, Kurinov I, Bode AM, Dong Z. The crystal structure of the active form of the C-terminal kinase domain of mitogen- and stress-activated protein kinase 1. J Mol Biol. 2010 May 28;399(1):41-52.

Reitinger S, Yu Y, Wicki J, Ludwiczek M, **D'Angelo I**, Baturin S, Okon M, Strynadka NC, Lutz S, Withers SG, McIntosh LP. Circular permutation of Bacillus circulans xylanase: a kinetic and structural study. Biochemistry. 2010 Mar 23;49(11):2464-74.

Capyk JK*, **D'Angelo I***, Strynadka NC, Eltis LD. Characterization of 3-ketosteroid 9{alpha}-hydroxylase, a Rieske oxygenase in the cholesterol degradation pathway of Mycobacterium tuberculosis. J Biol Chem. 2009 Apr 10;284(15):9937-46. ***: equal contribution**

Yam KC*, **D'Angelo I***, Kalscheuer R, Zhu H, Wang JX, Snieckus V, Ly LH, Converse PJ, Jacobs WR Jr, Strynadka N, Eltis LD. Studies of a ring-cleaving dioxygenase illuminate the role of cholesterol

metabolism in the pathogenesis of Mycobacterium tuberculosis. PLoS Pathog. 2009 Mar;5(3) ***: equal contribution**

Welti S, Fraterman S, **D'Angelo I**, Wilm M, Scheffzek K. The sec14 homology module of neurofibromin binds cellular glycerophospholipids: mass spectrometry and structure of a lipid complex. J Mol Biol. 2007 Feb 16;366(2):551-62.

**D'Angelo I**, Welti S, Bonneau F, Scheffzek K. A novel bipartite phospholipid-binding module in the neurofibromatosis type 1 protein. EMBO Rep. 2006 Feb;7(2):174-9.

## PEER review work:

Main author in a published review work focusing on the development of multispecific therapeutic antibodies. Invited by Teseo Editors, Pisa, Italy.

Main reviewer of computational investigations around Machine Learning applications aimed at discovering new small molecule inhibitors against SARS-Cov2. Invited by Prof. Dr. S. Pignattelli (Amgen, Milan, Italy).

## PATENTS (Published and Recent Applications)

Multitargeting bispecific antigen-binding molecules of increased selectivity. 32243/55787 A-2644-US-PSP-2. Filed August 2021

IL13 antigen binding proteins. USPO application WO/2021/021676. Publication date: 04.02.2021

Checkpoint inhibitor bispecific antibodies. USPO application #:62/530436. Submitted 10/07/2017

Anti PD-L1 / anti TIM3 bispecific antibodies. USPO application #:62/484025. Submitted 11/04/2017

Multivalent Heteromultimer Scaffold Design And Constructs. Publication #: WO2012/116453 Publication date: 07/09/2012

Multivalent Heteromultimer Scaffold Design And Constructs. Publication #: WO2014/012082 Publication date: 16/01/2014

Stable heterodimeric antibody design with mutations in the fc domain. WO2012/058768 and Publication date: 10/05/2012

Antibodies with Enhanced or Suppressed Effector Function. Publication #: WO2011/120135 (6-Oct-2011) Publication date: 06/10/2011

Antibodies with enhanced or suppressed effector function. Publication #: WO2011/120134 and Publication date: 06/10/2011

Heteromultimer constructs of immunoglobulin heavy chains with mutations in the fc domain. Publication #: WO2013/166594 and Publication date: 14/11/2013

Immunoglobulin constructs comprising selective pairing of light and heavy chains. Publication #:US2013051747 and Publication Date: 03/03/20

## TEACHING AND MENTORING (2018 to present day)

**University Lecturer:** Introduction to large molecule development and design for the biopharmaceutical industry. MSc in Biotechnology. Ma3 1-6, 2021. University of Pavia, Italy.

**University Lecturer:** Application of AI to enable enhanced molecule developability predictions. MSc in Biotechnology. Mar 31, 2020. Technical University of Northwest Switzerland (FHNW) , Basel, Switzerland

**University Lecturer:** Introduction to large molecule development and design for the biopharmaceutical industry. MSc in Biotechnology. May 6-8, 2020. University of Pavia, Italy.

**University Lecturer:** Introduction to large molecule development and design. MSc in Biotechnology. April 29-May 3, 2019. University of Pavia, Italy.

**University Lecturer**: Molecular engineering and therapeutic development. MSc in Biotechnology. October 26, 2018. University of Piemonte Orientale, Novara, Italy.