



# Best Practice Research Collaboration



**Boehringer Ingelheim**

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**Oncology Research**

**Medical University of Vienna**

**Prof. Michael Bergmann**

**Translational Tumorimmunology**

**Department of Visceral Surgery**

# Boehringer Ingelheim at a glance

- An independently and family-owned company
- One of the top 20 innovation-based biopharmas

€21.9  
billion



Net sales human pharma.

€5.7 billion reinvested in human pharma R&D.

6 focus  
areas



Cardiovascular-renal-metabolic, immunology, mental health, oncology, respiratory and eye health.

66  
million



patients reached around the world.

54,500  
employees



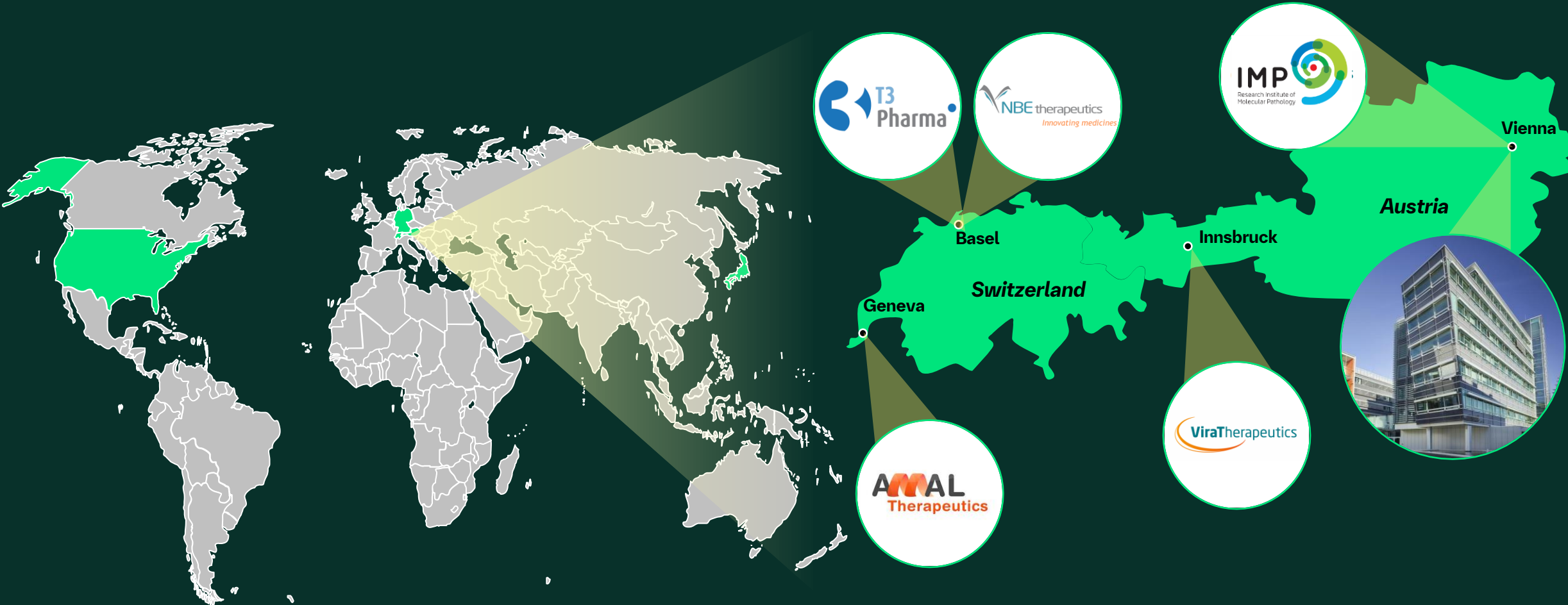
~11,500 in Human Pharma R&D and Animal Health.



Source: Boehringer Ingelheim Annual Report 2024



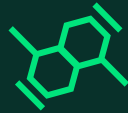
# Regional Center Vienna: a unique ecosystem focused on oncology research



# Boehringer Ingelheim collaboration frameworks

## Early Stage

**Fostering emerging science and accelerating new medicines.**



### opnMe.com

Fosters academic research with free molecules, research funding for collaborative proposals, and identified postdoc talents.



### Basic Science

Sponsors/funds academic institutions driving innovation.

We're the main sponsor of the Research Institute of Molecular Pathology (IMP) – one of the European hotspots for molecular biology



### Research Beyond Borders

Explores new therapeutic concepts and technologies in emerging areas.

## Later Stage



### Grass Roots

Mentors the next generation of life-science entrepreneurs.



### Business Development & Licensing

Focuses on New Molecular Entity (NME) portfolio impact through biotech, pharma and academic partnerships.

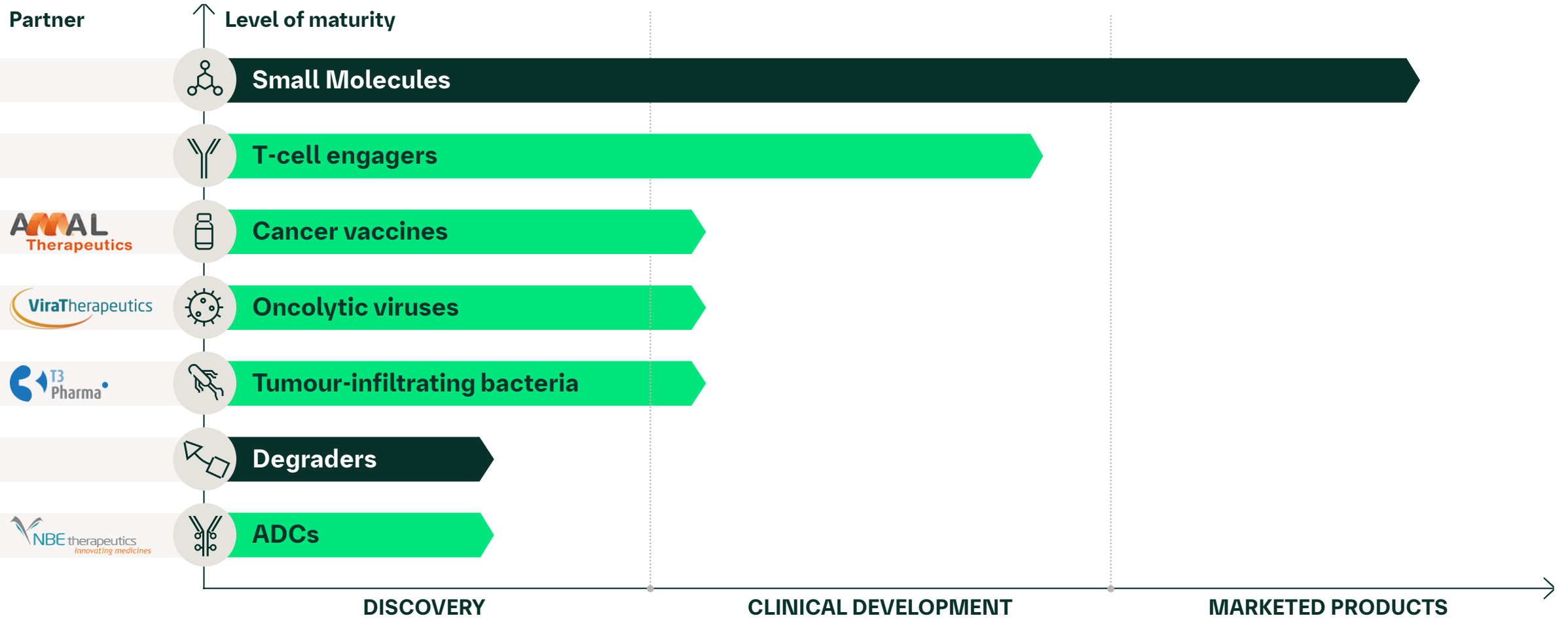


### Corporate Venture Fund

Makes investments in early-stage science and technology.

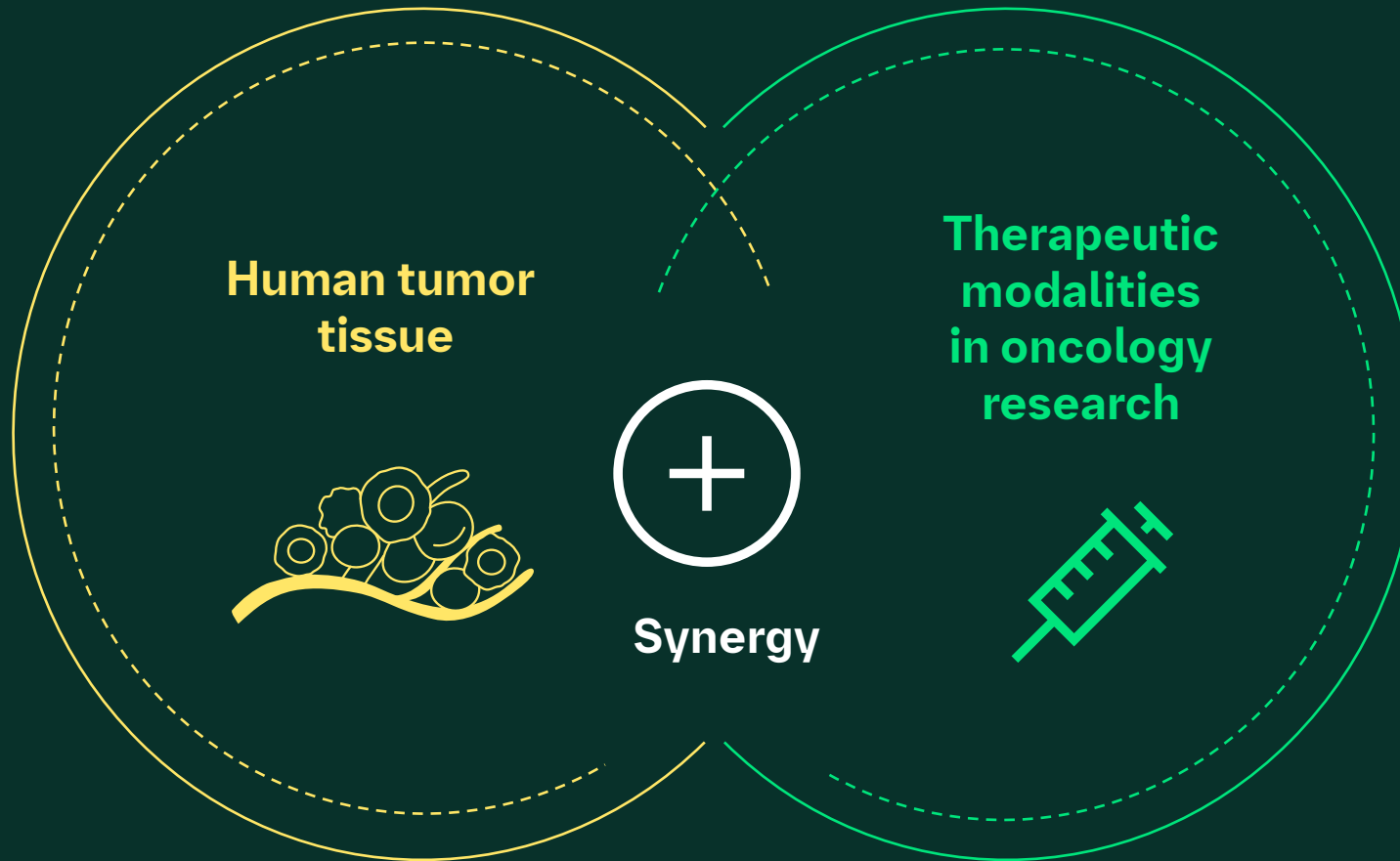
# Therapeutic Modalities in Oncology Research

Chemical  
Biological



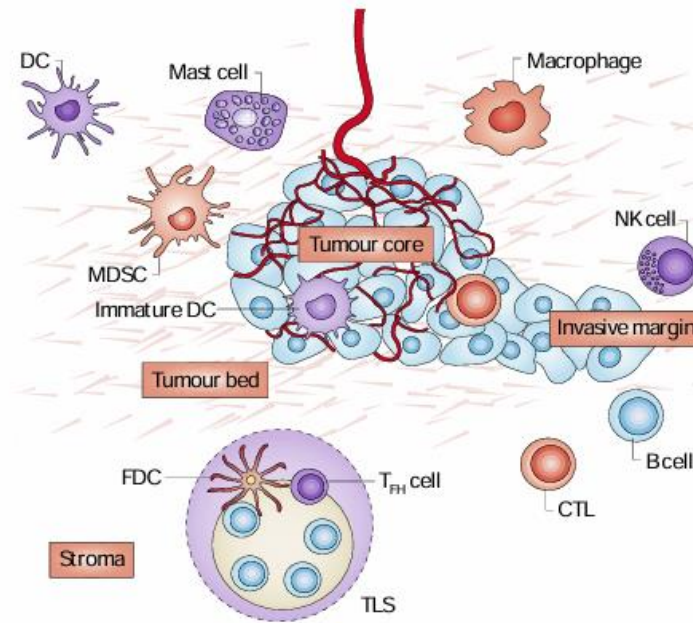
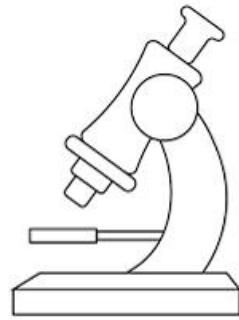
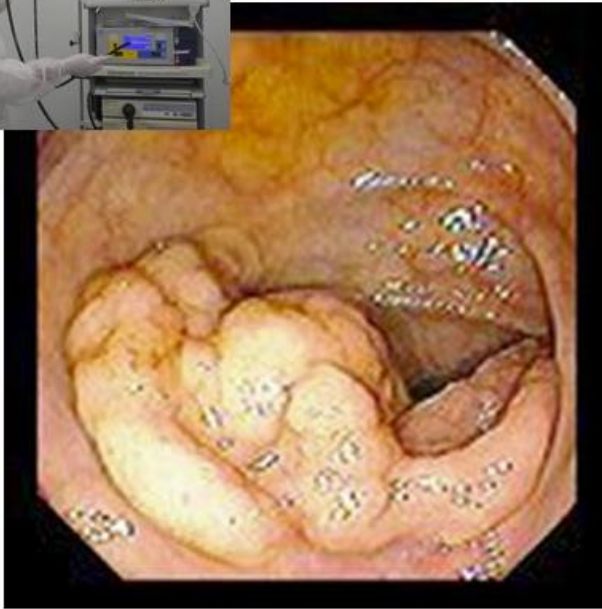
# Research collaboration

## Testing oncology compounds in human tumor tissue





# The Tumor Microenvironment is Different in Mouse and Man

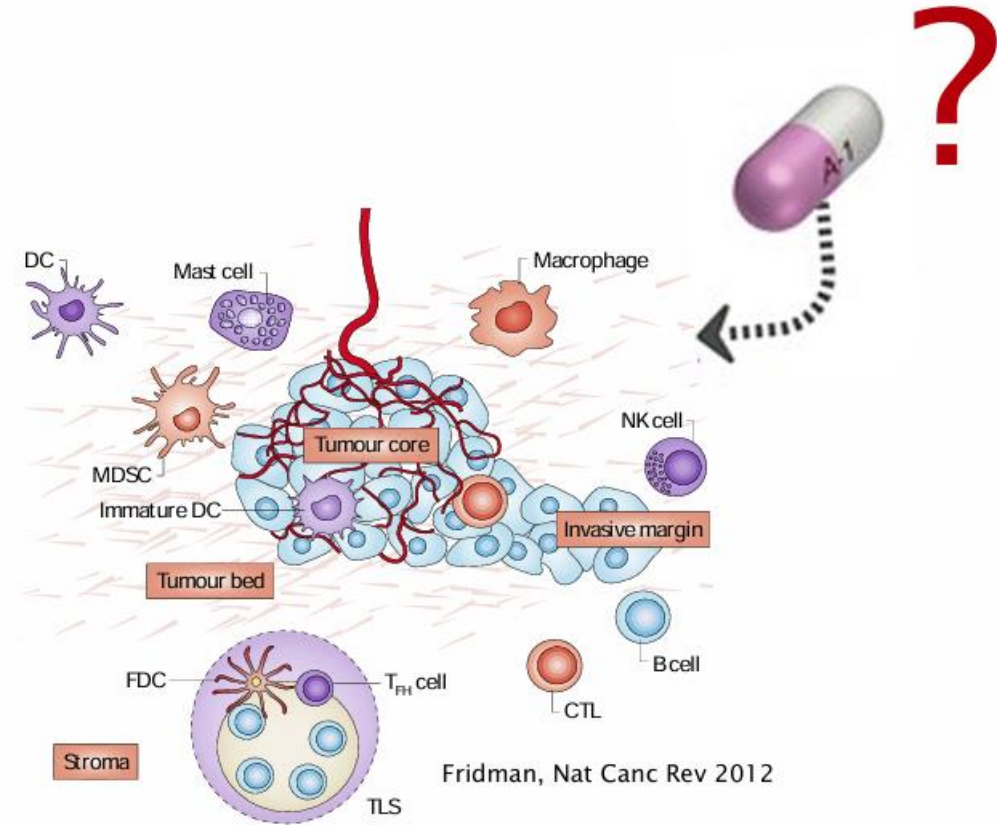


Fridman, Nat Canc Rev 2012

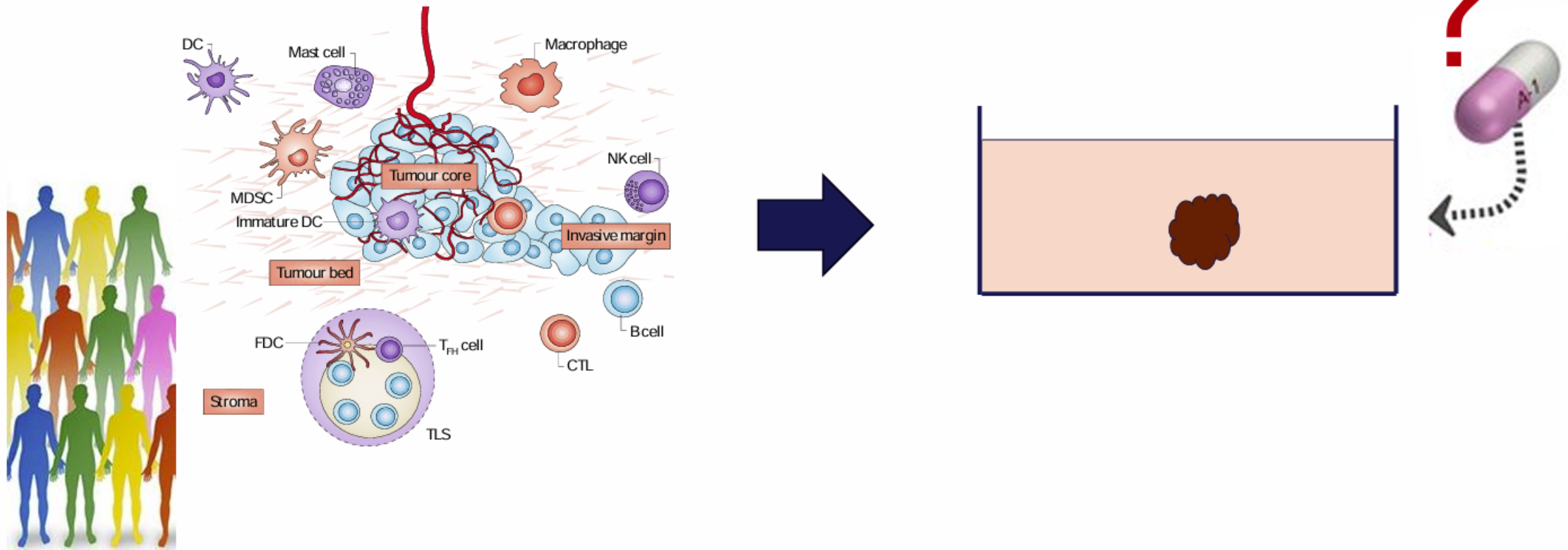




# Understand the Effect of Drugs on Human Tumor Tissue



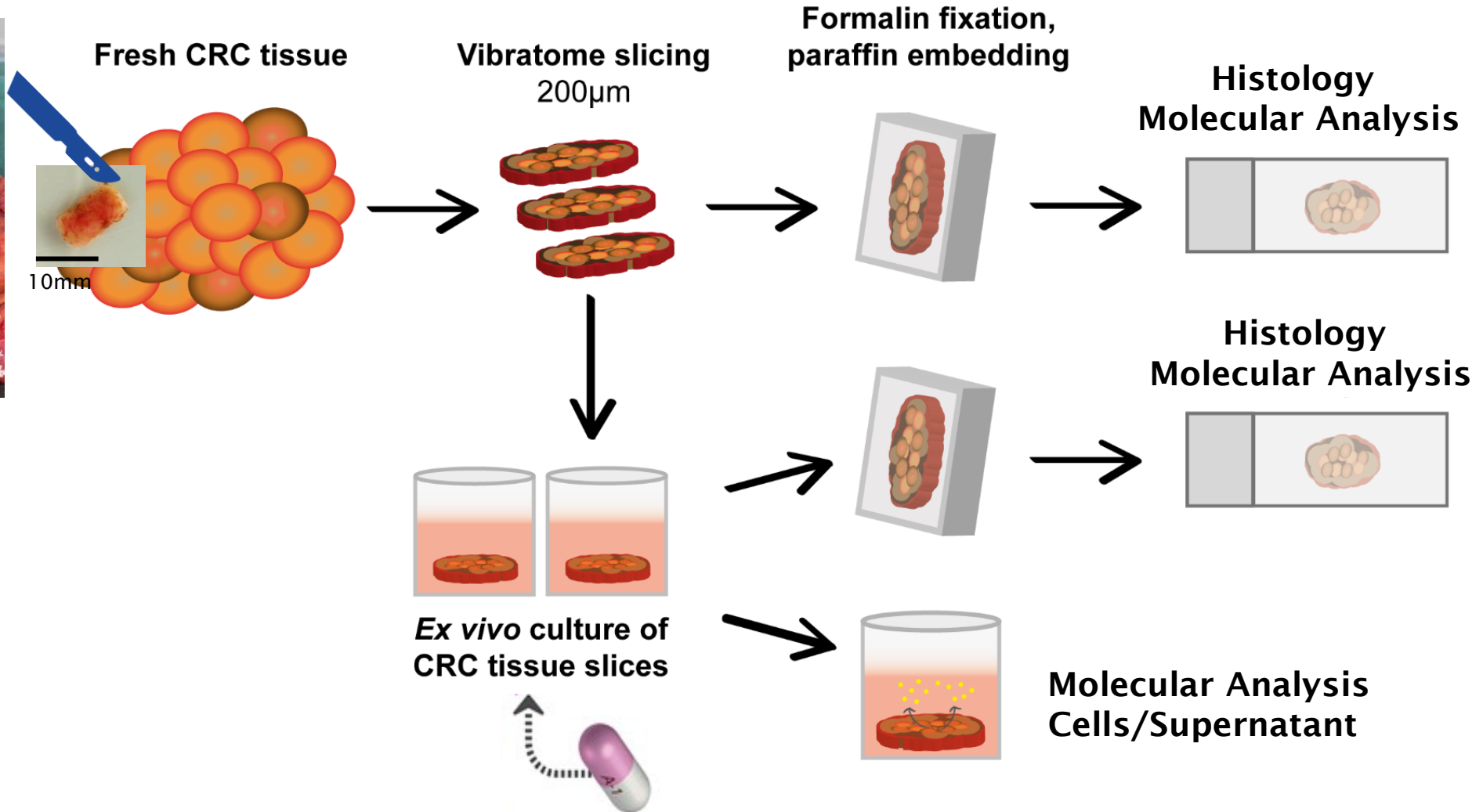
# Scientific Need: “Human Cancer in the Dish” Model



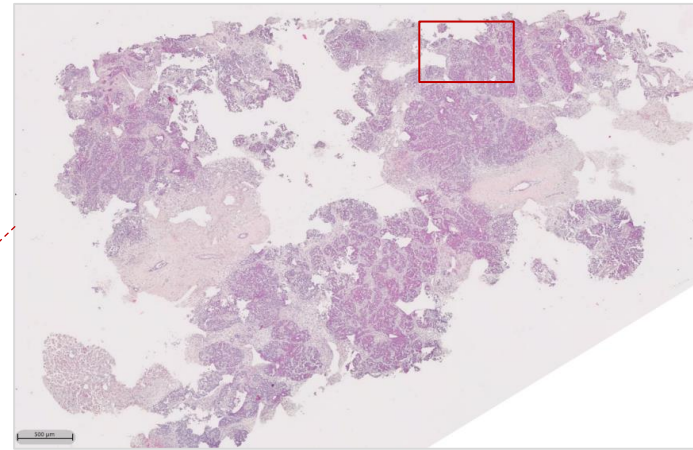
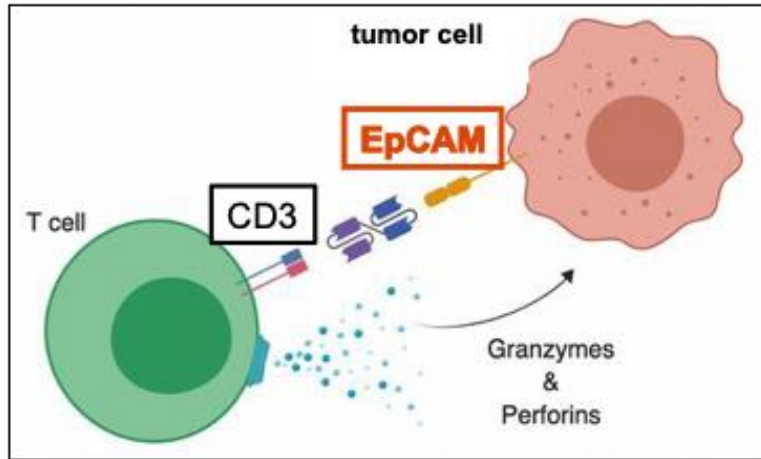
# Concept of Durg testing in Patient-Derived Tumor Slice Cultures



**Surgical Specimen**



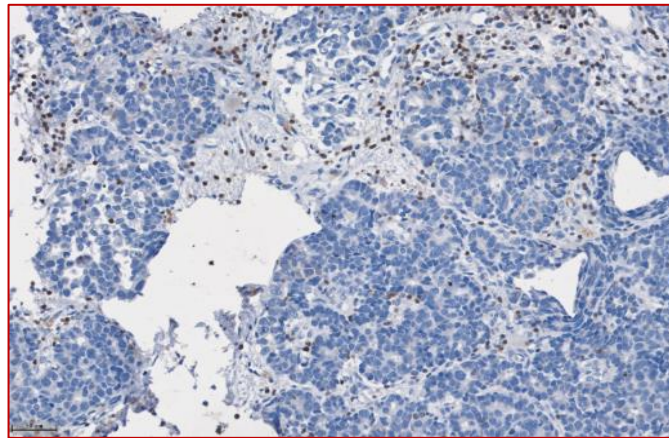
# Bi-specific Antibodies – A Novel Concept in Immunotherapy



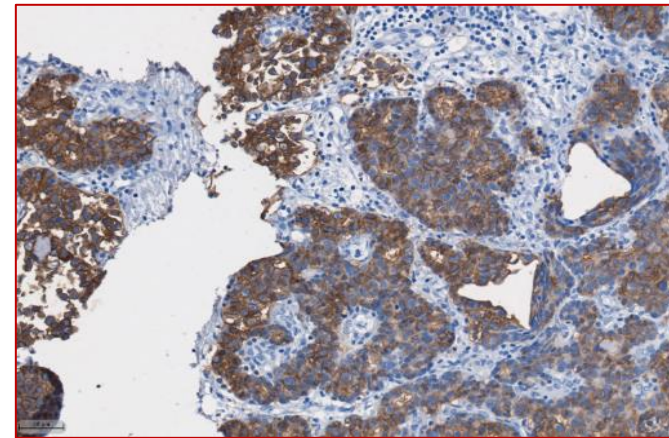
Baseline IHC  
CD3: positive  
EpCAM: positive

zoom-in

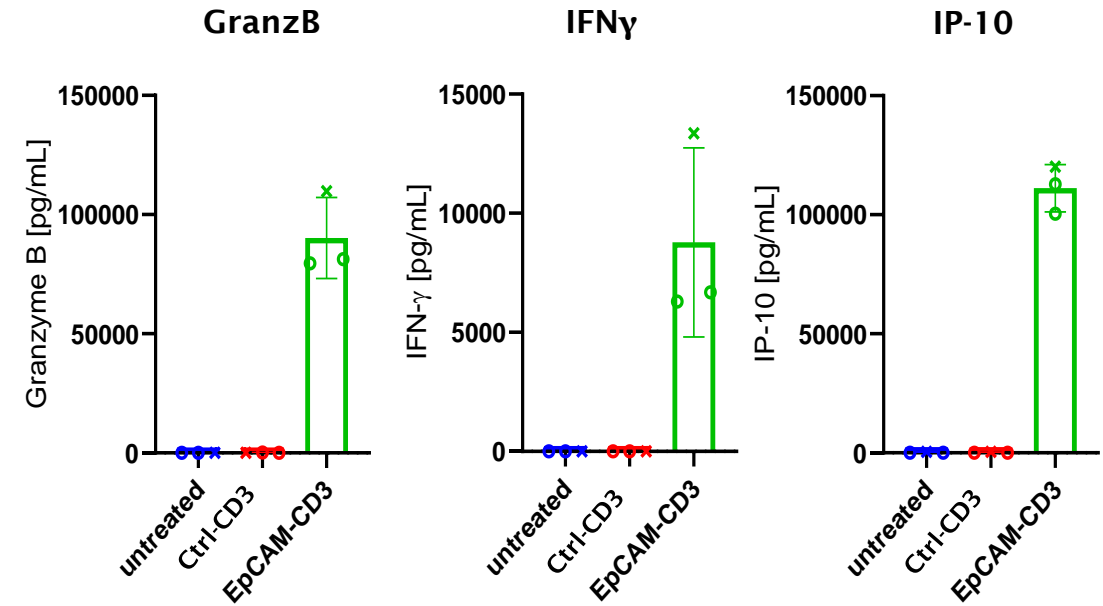
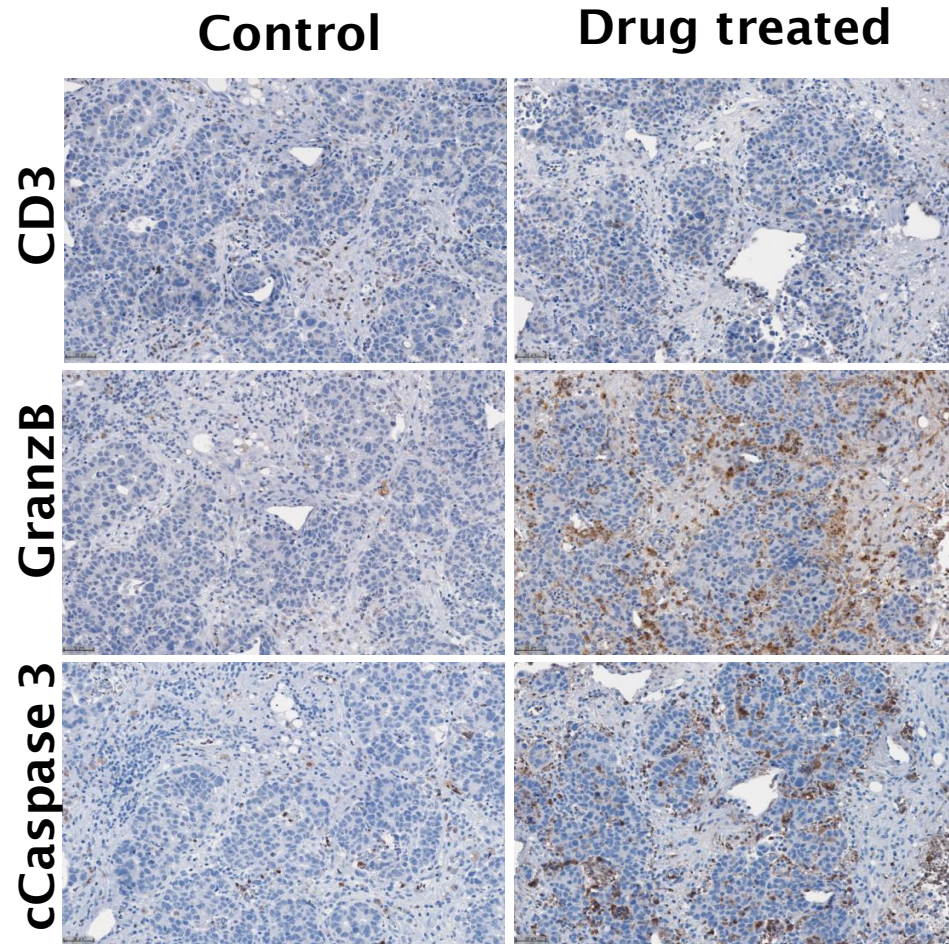
CD3



EpCAM



# Personalized Immunogenic Effects of Bi-specific Antibodies on Colorectal Cancer Tissue



**Induction of Immune Mediators in the Culture Supernatant**

**Immune Activation and Cell Death Induction**

# Joint High Impact Publications



CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

## A Novel B7-H6–Targeted IgG-Like T Cell–Engaging Antibody for the Treatment of Gastrointestinal Tumors

Wei Zhang<sup>1</sup>, Aurélie Auguste<sup>2</sup>, Xiaoyun Liao<sup>3</sup>, Christian Walterskirchen<sup>4</sup>, Kathrin Bauer<sup>5</sup>, Yu-Hsi Lin<sup>1</sup>, Ling Yang<sup>1</sup>, Farzaneh Sayedian<sup>5</sup>, Markus Fabits<sup>6</sup>, Michael Bergmann<sup>6</sup>, Carina Binder<sup>7</sup>, Leticia Corrales<sup>4</sup>, Anne B. Vogt<sup>4</sup>, Lindsey J. Hudson<sup>8</sup>, Martin P. Barnes<sup>8</sup>, Arnima Bisht<sup>9</sup>, Craig Giragossian<sup>10</sup>, Vladimir Voynov<sup>10</sup>, Paul J. Adam<sup>1</sup>, and Susanne Hipp<sup>1,11</sup>



### ABSTRACT

**Purpose:** Advanced-stage gastrointestinal cancers represent a high unmet need requiring new effective therapies. We investigated the antitumor activity of a novel T cell–engaging antibody (B7-H6/CD3 ITE) targeting B7-H6, a tumor-associated antigen that is expressed in gastrointestinal tumors.

**Experimental Design:** Membrane proteomics and IHC analysis identified B7-H6 as a tumor-associated antigen in gastrointestinal tumor tissues with no to very little expression in normal tissues. The antitumor activity and mode of action of B7-H6/CD3 ITE was evaluated in *in vitro* coculture assays, in humanized mouse tumor models, and in colorectal cancer precision cut tumor slice cultures.

**Results:** B7-H6 expression was detected in 98% of colorectal cancer, 77% of gastric cancer, and 63% of pancreatic cancer tissue samples. B7-H6/CD3 ITE-mediated redirection of T cells toward

B7-H6–positive tumor cells resulted in B7-H6–dependent lysis of tumor cells, activation and proliferation of T cells, and cytokine secretion in *in vitro* coculture assays, and infiltration of T cells into tumor tissues associated with tumor regression in *in vivo* colorectal cancer models. In primary patient–derived colorectal cancer precision-cut tumor slice cultures, treatment with B7-H6/CD3 ITE elicited cytokine secretion by endogenous tumor-infiltrating immune cells. Combination with anti-PD-1 further enhanced the activity of the B7-H6/CD3 ITE.

**Conclusion:** These data highlight the potential of the B7-H6/CD3 ITE to induce T cell–redirected lysis of tumor cells and recruitment of T cells into noninflamed tumor tissues, leading to antitumor activity in *in vitro*, *in vivo*, and human tumor slice cultures, which supports further evaluation in a clinical study.

### Introduction

Gastrointestinal cancers including colorectal, gastric, and pancreatic cancer remain a leading cause of cancer-related deaths in both men and women worldwide with more than 900,000, 760,000, and 466,000 deaths, respectively, every year (1–3).

Bispecific T-cell engagers represent a promising class of antibody-based cancer immunotherapy. These biotherapeutics are designed to facilitate the formation of a cytolytic synapse by binding concomitantly to an antigen on the tumor cells and to CD3 on T cells and direct the cytolytic activity of the T cells selectively to the tumor cells. After formation of the cytolytic synapse, the T cells increase the secretion of perforin and granzyme B, resulting in apoptosis of the tumor cells. Subsequent activation and proliferation of T cells leads to transient release of cytokines, which attracts other immune cells to the tumor tissue and has the potential to broaden the immune response against the tumor cells and convert a noninflamed (cold) into an inflamed (hot) tumor environment (4–9). While the first bispecific T-cell engagers targeted mostly lineage antigens in hematologic cancers and utilized the short half-life BiTE format which was administered via continuous intravenous infusion (10, 11), the next generation of T-cell engagers are based on bispecific formats incorporating half-life extension for increased dosing convenience and target novel antigens on solid tumors (6, 8, 9, 12–16). After the successful development of T-cell–engaging therapies in hematologic tumors (10, 11), the proof of principle for treatment of patients with solid tumors was demonstrated only recently. In a phase III trial, treatment of patients with metastatic uveal melanoma with tebentafusp, an HLA-A\*02:01/gp100/CD3 ImmTAC molecule, led to longer overall survival compared with the control group and was recently approved by the FDA (17).

However, for gastrointestinal tumors, the identification of tumor-associated antigens to ensure a therapeutic window remains challenging. In a phase I clinical trial with solitomab, an EpCAM targeting BiTE, in patients with solid tumors, treatment was associated with dose-limiting toxicities including severe diarrhea and increased liver enzymes, which is most likely associated to the expression of EpCAM in various healthy epithelial tissues including colon, small intestine, and hepatoblasts (18, 19). Treatment with MEDI-565, a BiTE targeting

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**Prior presentation:** Parts of this study have been presented at the AACR Annual Meeting 2021.

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Clin Cancer Res 2022;28:5190–201

doi: 10.1158/1078-0432.CCR-22-2108

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AACR American Association for Cancer Research

AACRJournals.org | 5190

frontiers | Frontiers in Immunology

TYPE Original Research  
PUBLISHED 08 September 2022  
doi:10.3389/fimmu.2022.1008764



### OPEN ACCESS

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**SPECIALTY SECTION**  
This article was submitted to  
Cancer Immunology  
and Immunotherapy,  
a section of the journal  
Frontiers in Immunology

**RECEIVED 01 August 2022**  
**ACCEPTED 17 August 2022**  
**PUBLISHED 08 September 2022**

**CITATION**  
Corrales L, Hipp S, Martin K, Sabarth N,  
Tirapu I, Fuchs K, Thaler B,  
Walterskirchen C, Bauer K, Fabits M,  
Bergmann M, Binder C, Chetta PML,  
Vogt AB and Adam PJ (2022) LY6G6D  
is a selectively expressed colorectal  
cancer antigen that can be used for  
targeting a therapeutic T-cell response  
by a T-cell engager.  
*Front. Immunol.* 13:1008764.  
doi: 10.3389/fimmu.2022.1008764

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## LY6G6D is a selectively expressed colorectal cancer antigen that can be used for targeting a therapeutic T-cell response by a T-cell engager

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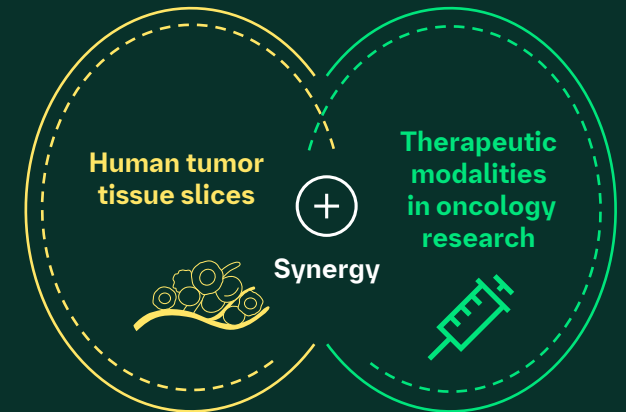
Colorectal cancer (CRC) is one of the most common cancers worldwide and demands more effective treatments. We sought to identify tumor selective CRC antigens and their therapeutic potential for cytotoxic T-cell targeting by transcriptomic and immunohistochemical analysis. LY6G6D was identified as a tumor selectively expressed CRC antigen, mainly in the microsatellite stable (MSS) subtype. A specific anti LY6G6D/CD3 T cell engager (TcE) was generated and demonstrated potent tumor cell killing and T cell activation *in vitro*. *Ex vivo* treatment of primary patient–derived CRC tumor slice cultures with the LY6G6D/CD3 TcE led to IFN $\gamma$  secretion in LY6G6D positive tumor samples. *In vivo*, LY6G6D/CD3 TcE monotherapy demonstrated tumor regressions in pre-clinical mouse models of engrafted human CRC tumor cells and PBMCS. Lastly, 2D and 3D cocultures of LY6G6D positive and negative cells were used to explore the bystander killing of LY6G6D negative cells after specific activation of T cells by LY6G6D positive cells. LY6G6D/CD3 TcE treatment was shown to lyse target negative cells in the vicinity of target positive cells through a combined effect of IFN $\gamma$ , TNF $\alpha$  and Fas/FasL. In summary, LY6G6D was identified as a selectively expressed CRC antigen that can be utilized to potently re-direct and activate cytotoxic T-cells to lyse LY6G6D expressing CRC using a TcE. This effect can be spread to target negative neighboring tumor cells, potentially leading to improved therapeutic efficacy.

### KEYWORDS

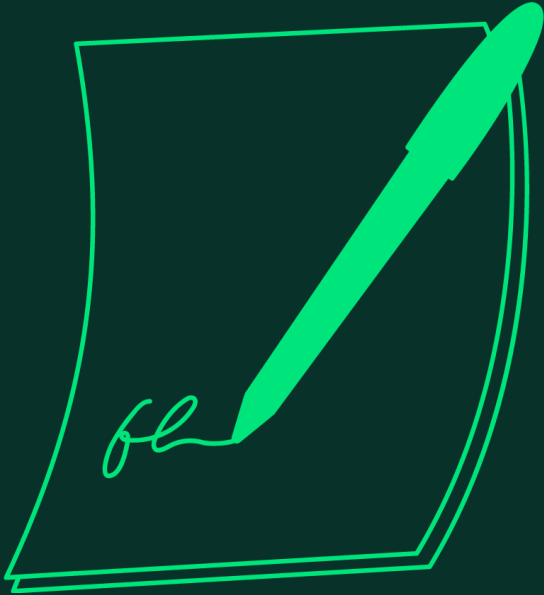
LY6G6D, CD3, TcE (T cell engager), CRC (colorectal cancer), immunotherapy

# Outcome of research collaboration: Characterization of oncology compounds in human tumor tissue slices

- **Proof of molecular concept** in human primary tissue
- **Characterization of response** human in primary tissue
- Exploration of **molecular markers**
- Demonstration of effective **combination** of therapeutic modalities
- Understanding **variability of patients**



# Research Agreement



## Workplan

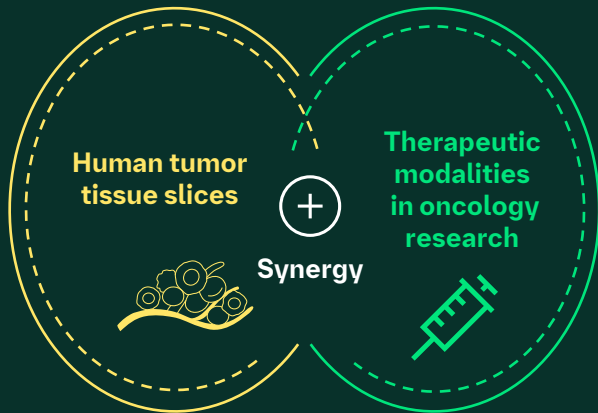
- Workpackages and clearly defined deliverables
- Costs
- Timelines

## Contract

- Confidentiality
- Right of Use / ownership of data
- Rules for publication
- Intellectual property
- Communication
- Reports, transfer of material
- Terms, termination and effect of termination

# What is key to drive a successful collaboration

- Being aligned on **common goal** and **expectations**
- Open, frequent and candid **communication**
- **Agility:** possibility to adjust project plan
- **Co-localisation** increases efficiency,  
e.g. transfer of compounds, F2F meetings
- **Complimentarity and Diversity,** in background and expertise



# Acknowledgements



## **Bergmann Lab**

**Markus Fabits**

Daphni Ammon

Brigitte Wolf

Carolina Klicka

Anne-Sophie Ebner

Anna Theophil

Askin Kulu

**Michael Bergmann**

## **AKH**

Gastrointestinal Group

Clinical Institute of Pathology

## **Boehringer-Ingelheim RCV**

**Anne Vogt** (Research collaboration)

Project leaders



## **MUW Core Facilities**

### **Farlik-Födinger Lab**

Peter Traxler

**Matthias Farlik-Födinger**

