

# PBSS Symposium:

## Preclinical Models to Guide Therapeutic Development in Oncology

**Speakers:** Maryland Franklin (Covance-Preclinical Oncology), Karen Rex (Amgen), Michael Alonso (Bolt Biotherapeutics), Saul Priceman (City of Hope), Saul Kivima (Nektar), John Langowski (Kite Pharma), Yorick Post (Hubrecht Institute - Hans Clevers Group; currently Surrozen), Philippe Depeille (UCSF), Mark Merchant (Genentech)

**Organizers:** Gregory Wagner and Betty Chang

**Date/Time:** 2020-03-09, 8:45-17:00 Pacific Time

**Registration fee (USD):** Regular: \$195; Academic: \$125; Students & Unemployed: \$35

**Location:** San Francisco Bay Area: Foster City Crowne Plaza

**Registration:** <http://www.pbss.org/asp/eventInfo.aspx?eID=668>

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This PBSS symposium will provide an overview of the use of preclinical models for guiding development of new therapeutic agents for oncology. A variety of in vivo approaches have been successfully used for traditional chemotherapeutic agents and target-based small molecule and antibody-based therapeutic agents. These include the more well established in vivo rodent models utilizing immune-compromised xenograft tumor implants, orthotopic tumor models and use of patient-derived (PDX) cell lines in xenograft models.

In recent years, newer therapeutic approaches have emerged with improved clinical efficacy, such as checkpoint inhibitors and CAR-T cell-based therapeutics, which target the tumor microenvironment (TME) and the immune system. New preclinical models have also been developed which provide higher throughput and allow a more refined characterization of these emerging therapies. In vivo examples include improved syngeneic models (which are immune competent), improved imaging modalities that provide real time data on anatomical location and extent of tumor burden, and multiplexed immunohistochemistry. In vitro test systems have been developed which provide a better recapitulation of the human TME than traditional rodent models. Examples include 3D systems which can incorporate human immune cells and organoids containing genetically-modified, human-derived cells. This symposium will provide insights from scientists experienced in using these preclinical models.

### List of Speakers and Presentations (order of presentations TBD):

- **Symposium Overview and Relevance to Contemporary Issues in Development of Therapeutic Agents for Oncology** (Mark Merchant, Genentech)
- **Preclinical Mouse Models for Oncology and Immuno-oncology Applications** (Maryland Franklin, Covance-Preclinical Oncology)
- **Preclinical development of AMG 510, a first-in-human covalent inhibitor of KRASG12C for the treatment of advanced solid tumors** (Karen Rex, Amgen)
- **Case Study: Bench to Bedside with Immune Stimulating Antibody Conjugates (ISAC)** (Michael Alonso, Bolt Biotherapeutics)
- **Preclinical investigation of NKTR-255, a polymer conjugated IL-15 with potent NK cell activation and anti-tumor activity in combination with tumor targeting antibodies.** (Saul Kivimaa, Nektar)
- **Advancing CAR T Cell Therapy for the Treatment of Solid Tumors** (Saul Priceman, City of Hope)
- **The Utility of Preclinical Models in Development of CAR T** (John Langowski, Kite Pharma)
- **Current Status in the Application of Organoids to Oncology Drug Discovery and Biomarker Identification** (Yorick Post, Hubrecht Institute - Hans Clevers Group; currently Surrozen; Philippe Depeille, UCSF)

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## Presentation Details

- **Preclinical Mouse Models for Oncology and Immuno-oncology Applications** (Maryland Franklin, Covance-Preclinical Oncology)

**Synopsis:** This presentation will provide an overview of the mouse models used in preclinical oncology and immuno-oncology studies. It will discuss the pros and cons of the various models and further outline approaches for model selection, model characterization and model utilization. In addition, the presentation will cover the benefits of incorporating small animal radiation and small animal in vivo imaging into preclinical oncology and immuno-oncology studies.

- **Preclinical development of AMG 510, a first-in-human covalent inhibitor of KRASG12C for the treatment of advanced solid tumors**

(Karen Rex, Amgen)

**Synopsis:** KRAS is the most frequently mutated oncogene in cancer and encodes a key signaling protein in tumors. The KRAS(G12C) mutant has a cysteine residue that has been exploited to design covalent inhibitors that have promising preclinical activity. Amgen has developed AMG 510, an orally bioavailable, covalent inhibitor of KRASG12C with potent biochemical and cellular activity in addition to robust in vivo efficacy as a single agent and in combination with cytotoxic or targeted agents in KRAS G12C tumors. AMG 510 results in an inflamed tumor microenvironment, boosts sensitivity to checkpoint inhibition, and drives durable cures in syngeneic models of multiple KRAS mutants. Data will be presented from preclinical models related to characterization of the effects of AMG 510 on the tumor microenvironment, including demonstration of in vivo tumor regression, which led to advancement of the molecule to clinical development.

- **Case Study: Bench to Bedside with Immune Stimulating Antibody Conjugates (ISAC)** (Michael Alonso, Bolt Biotherapeutics)

**Synopsis:** Bolt Biotherapeutics' ISAC platform harnesses the ability of toll-like receptor (TLR) agonists to convert cold tumors into immunologically hot tumors following systemic administration. The presentation will include an overview of the unmet clinical need and a brief history of Bolt's research and development pathway. In particular, data will be presented on the challenges involved in using preclinical animal models to characterize the pharmacological profile of novel therapeutic agents such as Bolt's ISAC.

- **Preclinical investigation of NKTR-255, a polymer conjugated IL-15 with potent NK cell activation and anti-tumor activity in combination with tumor targeting antibodies.** (Saul Kivimae, Nektar)

**Synopsis:** IL-15 is a cytokine that activates and provides survival benefit to NK cells. Exploiting the therapeutic value of native IL-15 has been challenging due to its unfavorable pharmacokinetic properties and tolerability. NKTR-255 is a polymer-conjugated human IL-15 that retains binding affinity to the alpha subunit of IL-15 receptor and exhibits reduced clearance to provide a sustained pharmacodynamic response. NKTR-255 has potential for providing an enhanced immunotherapeutic effect when combined with monoclonal antibodies that mediate tumor killing by antibody-dependent cellular cytotoxicity (ADCC). Here we investigate the pharmacological properties of NKTR-255 on NK cells and demonstrate the therapeutic effect of NKTR-255 when combined with tumor-directed monoclonal antibodies in preclinical human lymphoma model.

- **Advancing CART Cell Therapy for the Treatment of Solid Tumors** (Saul Priceman, City of Hope)

**Synopsis:** This presentation will focus on recent advances in CAR T cell therapy, and highlight developments in the field to overcome the major challenges hampering an effective immunotherapy, which are largely defined by tumor heterogeneity and the immunosuppressive tumor microenvironment. Preclinical and clinical experiences will be presented to show utility of more relevant preclinical studies that may inform on early phase clinical trials in patients with solid tumors. An update on City of Hope's solid tumor CAR T cell program will also be presented.

- **The Utility of Preclinical Models in Development of CART** (John Langowski, Kite Pharma)

**Synopsis:** The presentation will provide an overview of the research and development process for CAR-T, with examples provided from the preclinical development of Kite's Yescarta (axicabtagene ciloleuce). Yescarta is a first-in-class, FDA approved therapy for refractory diffuse large B cell lymphoma (DLBCL). The presentation will include a discussion of the utility of preclinical models for establishing pharmacological efficacy and safety, as well as a discussion of emerging technologies to augment the selectivity and regulate the activity of this therapy as the field advances towards solid tumor indications.

- **Current Status in the Application of Organoids to Oncology Drug Discovery and Biomarker Identification** (Yorick Post, Hubrecht Institute)

- Hans Clevers Group; currently Surrozen; Philippe Depeille, UCSF)

**Synopsis:** Historically, organoids or "mini-organs in a dish", were used to study stem cell biology of epithelial lineages and to model disease progression, and understand factors of the microenvironment in early development. Recent advances in organoids allow adult mammalian stem cells to exhibit their remarkable self-organizing properties, and the resulting organoids reflect key structural and functional properties of the organ. The speakers will review the recent progress in creating organoid model systems which better recapitulate human tissue, including the tumor microenvironment (TME), and how these systems are being applied to develop therapeutic agents for oncology. Some of the items which will be covered include the following:

- Patient-derived tumor organoids which can maintain key features and characteristics of tumor tissue, thereby providing a novel preclinical platform for personalized screening of therapeutics.
- The addition of autologous immune cells to the patient-derived tumor organoids allowing for the interrogation of the therapeutics on the immune system and TMI.
- Use of patient-derived tumor organoids as preclinical pharmacology models to characterize and optimize novel cancer therapeutics agents (such as agents acting via immuno-oncology mechanisms).
- Use of biomarkers to obtain personalized predictive/prognostic information.