

JAMES RENNIE BEQUEST

REPORT ON EXPEDITION / PROJECT / CONFERENCE

Expedition/Project/ Conference Title:	2025 International Mammalian Synthetic Biology Workshop
Travel Dates:	10-12 August, 2025
Location:	University of California, Irvine (USA)
Group member(s):	Alex Arrese-Igor
Aims:	Present our work with CHO as biofactories, learn the newest advances on mammalian synthetic biology, explore the funding and development situation of the field for post-PhD opportunities
Photography consent form attached: (please refer to your award letter)	☐ Yes ☒ No

OUTCOME (a minimum of 500 words):-

I recently had the opportunity to attend mSBW 2025, a leading international meeting in the field of synthetic biology and genetic engineering. This year, following the trend of the last half decade, there has been a strong emphasis on **advances in cellular therapies, particularly CAR-T cells**. One of the highlights was **Tim Lu's** presentation on SENTI-Bio, a company he co-founded that is advancing next-generation CAR-T therapies into clinical trials. His work demonstrated how rationally designed genetic circuits can give therapeutic cells enhanced specificity, safety, and adaptability, paving the way for engineered immune therapies to address previously intractable cancers. Alongside contributions from other leaders such as **Elena Sotillo (Stanford)**, who underlined the incredibly fast-paced advances in CAR designs, these talks underlined how cell therapies are moving rapidly from fundamental proof-of-concept towards real clinical application.

The increase in applications of synthetic biology tools was underlined as well by **Michael Elowitz (Caltech)**, a pioneer in the field. His talk explored pyroptosis as an alternative effector mechanism to apoptosis in engineered kill switches. This approach has significant implications for cancer immunotherapies, where stimulating the immune system is often as important as directly eliminating cancer cells. Elowitz also discussed "polytransfection scans" as a high-throughput strategy for mapping the combinatorial space of plasmid concentrations in mammalian cells. This methodology is particularly useful for studies involving programmable effectors such as dCas9-based systems, representing a significant contribution for my own research. Another relevant voice in the field, **Wendell Lim (UCSF)** underlined the vast array of genetic "commands" we have developed for the cell (expression – synNotch, proliferation/killing – CAR-T, ...) and how the next step is to combine these to solve complex, tissue-based diseases. In that regard, he presented a "brain GPS" for cell therapy, which targets specifically glioblastoma-specific proteins (BCAN), making the genetic circuit of the cell therapy much more specific, thus improving the screening in clinical trials.

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Another particularly relevant contribution came from **Carlos Llanos (Rice University)**, who presented work on feedback-responsive cell factories for dynamic modulation of the unfolded protein response (UPR). The UPR has long been a major bottleneck in the field of cell bioproduction, as accumulation of misfolded proteins triggers stress pathways that sharply reduce yields. By engineering synthetic circuits using the key regulators XBP1s and CHOP, Llanos and his team developed feedback loops that dynamically control UPR activity and improving protein production. Complementing these results, Llanos also described a **mathematical modelling framework** that predicts circuit performance based on measurable parameters such as transcription factor synthesis and degradation rates. His main conclusions—that genetic circuit topology determines sensitivity to parameter variation, and that high dynamic range is often incompatible with low basal activity—offer important lessons for the broader synthetic biology community, for more rational circuit design.

In addition, **Lacra Bintu (Stanford University)** presented an impressive screen of transcription factor effector domains for gene activation and repression. Of particular interest, she showed that alternative KRAB domains (such as those from ZNF705 and ZNF471) can outperform the standard ZNF10 domain in gene silencing. On the activation side, her group developed a novel tripartite activator (NFZ), which is significantly smaller and more efficient than commonly used activators like VPR. These advances provide valuable new tools for fine-tuning mammalian gene expression.

Beyond these talks, the conference showcased a rich array of innovative work. **Katie Galloway (MIT)** presented pioneering experimental results on “gene syntaxes,” confirming that gene arrangement—whether divergent, tandem, or convergent—can profoundly shape transcriptional outcomes. Her group demonstrated practical applications of these principles, including improving antibody production. Similarly, **George Chao (Harvard)** described a systematic comparison of 32 recombinases, mapping their specificity and cross-reactivity, which will serve as an invaluable reference for groups employing recombinase-based systems. Other notable contributions included **Xinyi Chen (Stanford)**, who introduced a novel trogocytosis-based delivery mechanism for transferring membrane proteins between immune cells, and **Karmella Haynes (Emory University)**, who presented a modular strategy for designing synthetic long non-coding RNAs inspired by the natural silencing function of Xist.

Overall, the conference provided a great platform for learning and networking. It offered the chance to hear first-hand about the latest advances in genetic circuit design, therapeutic applications, and bioproduction technologies, while also highlighting the challenges that remain. The poster sessions and informal discussions enabled me to exchange ideas with colleagues and experts from different perspectives, which was both stimulating and encouraging.

I am sincerely grateful to the James Rennie Bequest for supporting my attendance at this meeting. The insights I gained will have a direct impact on my PhD project. This experience has not only expanded my scientific understanding but has also provided valuable new contacts and perspectives that will help guide the next stages of my research career.