Big pharma seduced by transcription factors again. What has changed?

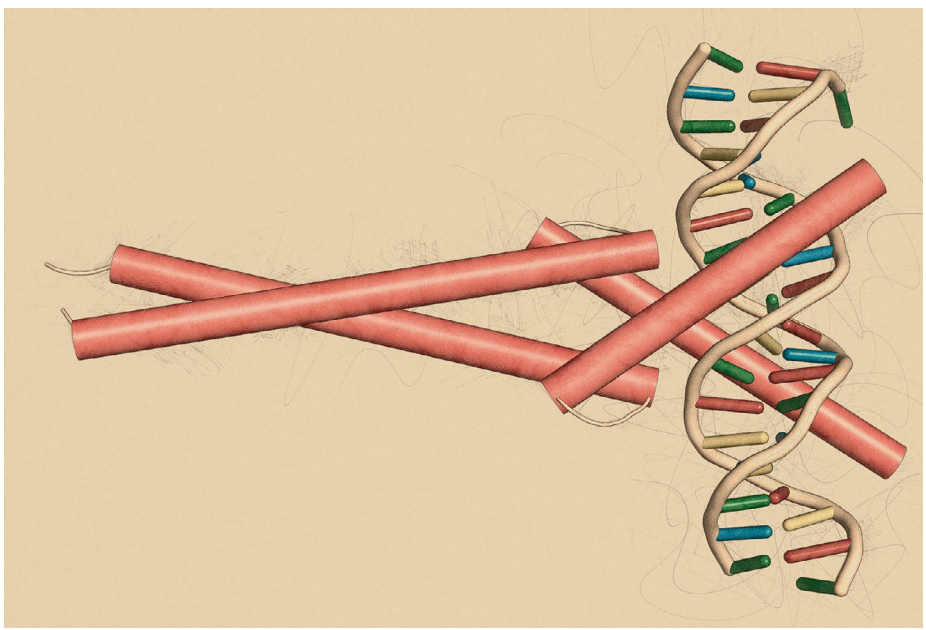
Long considered undruggable, transcription factors have finally become fair game for a clutch of innovative biotechs who are combining biological insights with innovative chemistry to bring into play a vast number of new drug targets.

By Cormac Sheridan

Transcription factors have been in drugmakers' crosshairs for decades. They control which genes are turned on or off, and targeting them could potentially tackle disease-causing proteins. Despite extensive efforts with programs directed at targets such as tumor-inducing MYC and the tumor suppressor p53, transcription factors have generally proved undruggable with conventional approaches. But with new therapeutic modalities, such as PROTACs (proteolysis-targeting chimeras), drugmakers have redoubled their efforts, bringing newer targets, such as signal transducer and activator of transcription 6 (STAT6), into play.

STAT6 is emerging as a potentially important therapeutic target for autoimmune and inflammatory conditions because it mediates the effects of the inflammatory cytokines interleukin (IL)-4 and IL-13. Kymera Therapeutics has developed a cereblon-based STAT6 degrader, KT-621, and recently released data from a phase 1 trial in human volunteers. Many other firms are following suit, with STAT6 becoming the focus of intense dealmaking activity this year. And the same holds for transcription factors in general, as large pharma firms approach these once challenging proteins with innovative discovery platforms.

The human proteome contains an estimated 1,600 transcription factors. Their role is to rev up – and occasionally to shut down – gene transcription by binding specific DNA sequences. Transcription factors act mostly within multiprotein complexes that include accessory proteins, co-activators and repressors. Targeting them has always been



Generative chemistry and simulations are speeding the study of transcriptiwon factors, such as MYC and MAX (pictured bound to DNA).

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News in brief

Vertex dives into covalent biologics

Enlaza Therapeutics and Vertex Pharmaceuticals have entered into a multi-drug discovery collaboration to develop Enlaza's covalent protein platform into first-in-class drugs for autoimmune diseases. The deal sees Enlaza receive $45 million up front with a further $2 billion available for future milestone payments.

Covalent medicines have many advantages: they bind targets irreversibly and result in increased efficiency and potency due to increased activation that results in prolonged activity and allows a reduced dosage. But covalent drugs to date have all been small molecules, and these are prone to off-target interactions.

Enlaza's proprietary technology aims to bring the advantages of covalent inhibitors to protein-based drugs. The approach is centered on proximity chemistry. It uses an unnatural amino acid, such as fluorosulfated tyrosine, that can be inserted into a protein drug during synthesis. When the engineered protein nears a binding partner, it forms an irreversible bond with the fluorosulfated tyrosine. Enlaza hopes this technology will generate a new class of protein therapeutics that takes advantage of the specificity of larger biologic agents and improves their ability to block signalling.

With Enlaza's approach, the unnatural amino acids remain latent and unreactive in vivo, only becoming active in proximity with the target, when they form permanent bonds with a target amino acid residue. In the case of fluorosulfated tyrosine, covalent bonds are formed via sulfur fluoride exchange (SuFEx) click chemistry with tyrosine, histidine or lysine residues.

Covalent protein drugs are not only smaller than antibodies – 15–30 kDa – but also overcome protein dissociation, usually a concern for antibody drug developers. Covalency stabilizes drug binding, while unbound therapeutics are cleared quickly.

Enlaza's platform has already shown promise in oncology. This new deal with Vertex will focus on developing covalently bonding drugs and T cell engagers for autoimmune diseases.

Table 1 | Selected drug development programs that target transcription factors

Company	Molecule	Mechanism	Indication(s)	Status
Merck	Welireg (belzutifan)	Hypoxia-inducible factor 2α inhibitor	Von Hippel–Lindau disease; advanced renal cell carcinoma; pheochromocytoma or paraganglioma	First FDA approval 2021
Roche	Giredestrant	ER degrader	ER^+ metastatic breast cancer	Phase 3
Moleculin Biotech	WP1066	STAT3 inhibitor	Glioblastoma	Phase 2
Tvardi Therapeutics	TTI-101	STAT3 inhibitor	Idiopathic pulmonary fibrosis	Phase 2
Peptomyc (Barcelona, Spain)	OMO-103	Cell-penetrating miniprotein that inhibits MYC by disrupting dimerization with its obligate binding partner MAX	Osteosarcoma	Phase 2
C4 Therapeutics	Cemsidomide (CFT7455)	Degrader of IKZF1 and 3	Non-Hodgkin's lymphoma; multiple myeloma	Phase 1/2
Halda Therapeutics	HLD-0915	RIPTAC ('regulated induced proximity targeting chimera') heterobifunctional molecule that promotes the formation of a non-functional complex between the androgen receptor and an undisclosed transcriptional regulator, which is essential for cell survival	Prostate cancer	Phase 1/2
IDP Pharma (Barcelona)	IDP-121	Stapled-peptide-based MYC inhibitor	Hematologic malignancies	Phase 1/2
Parabilis Medicines	FOG-001	α-helically locked 'Helicon' peptide that disrupts the interaction between β-catenin and the T cell factor family of transcription factors	Locally advanced or metastatic solid tumors	Phase 1/2
Sapience Therapeutics	Lucicebtide (ST101)	SPEAR ('stabilized peptide engineered against regulation') antagonist of C/EBPβ	Solid tumors	Phase 1/2
Flare Therapeutics	FX-909	Peroxisome proliferator-activated receptor-γ inhibitor	Solid tumors, including bladder cancer	Phase 1
Genentech	RO7656594	Oral androgen receptor degrader	Prostate cancer	Phase 1
Kymera Therapeutics	KT-621	STAT6 inhibitor	Atopic dermatitis	Phase 1
MiNA Therapeutics (London)	MTL-CEBPA	Small activating RNA that upregulates C/EBPα	Solid tumors	Phase 1
Nurix Therapeutics	NX-2127	Dual inhibitor of Bruton's tyrosine kinase and IKZF1 and 3	B cell malignancies	Phase 1
Remix Therapeutics	REM-422	Oral *MYB* mRNA degrader	High-risk myelodysplastic syndrome and acute myeloid leukemia	Phase 1
Vividion Therapeutics	VVD-850	STAT3 inhibitor	Solid and hematological tumors	Phase 1
Shanghai Chaoyang Pharmaceutical	HP-001	IKZF1 and 3 degrader	Hematologic malignancies	Phase 1

C/EBP, CCAAT/enhancer binding protein; ER, estrogen receptor; IKZF, Ikaros zinc finger protein; STAT, signal transducer and activator of transcription. Sources: ClinicalTrials.gov, PubMed and company websites.

a compelling prospect because these proteins are central role to the control of gene expression in eukaryotic cells and are often dysregulated in cancers, immunological conditions, congenital heart disease, neuropsychiatric disorders and other areas of disease.

In cancer, in particular, directly blocking a transcription factor, instead of blocking a signaling pathway stimulated by external signals, may reduce the likelihood of drug resistance emerging. "The general concept is, the closer you go to the nucleus, there's a hope that you prevent that type of resistance," says Bob Yauch, executive director, discovery oncology at Genentech. The extent to which transcription factors drive a cancer's lineage addiction – or dependency on a specific developmental pathway associated with the cells from which the tumor originated – is also attracting research attention. "The whole concept there is that tumors can really hijack and leverage some of the master regulatory factors that are important for survival of that lineage," he says. Targeting them may open up another line of attack.

Up until recently, however, the tools to drug most transcription factors were lacking. Most transcription factors do not possess the deep binding pockets that traditional drug hunters seek to exploit. (The main exceptions include members of the ligand-activated nuclear receptor superfamily, which includes both the androgen and estrogen receptors.) But recent innovations in small molecule chemistry, peptide design, chemoproteomics and structural biology have generated insights into how myriad transcription factors bind, and these have opened up new ways of modulating their activity, with, for example, PROTACs and other targeted protein degraders, molecular glues, and stabilized peptides.

Big pharma is interested. Paris-based Sanofi has entered drug discovery collaborations for immunological conditions with Belharra Therapeutics and Nurix Therapeutics. Genentech

also has an ongoing discovery pact with Belharra and has in-licensed an oral androgen receptor degrader from Shanghai Jemincare Pharmaceutical. Separately, its parent firm Roche, of Basel, Switzerland, has signed an oncology drug discovery deal with Flare Therapeutics. German pharma Boehringer Ingelheim has signed deals with Quantro Therapeutics and Ten63 Therapeutics.

STAT6 alone has been at the center of many deals. Gilead Sciences paid a hefty $250 million up front earlier this year to acquire Ballerup, Denmark-based Leo Pharma's preclinical portfolio of small molecule inhibitors and targeted protein degraders of STAT6. Sanofi exercised an option on Nurix's preclinical oral STAT6 inhibitor in June, as part of their wider alliance. The French pharma had previously licensed another oral STAT6 inhibitor program from Recludix Pharma, and a candidate, REX-8756, is due to enter clinical development shortly. Late last year, Johnson & Johnson licensed Tokyo-based Kaken Pharmaceutical's preclinical STAT6 inhibitor program.

But drug hunters are pursuing strategies that go beyond finding cryptic binding pockets to gain a molecular foothold on an otherwise slippery target. The field is also finding better ways of targeting transcription factors that have already been drugged. For example, Flare Therapeutics is moving toward the clinic with an androgen receptor degrader that selectively targets the active conformation of the protein, which only forms when its natural ligands – testosterone or its active metabolite, 5α-dihydrotestosterone – are bound. Existing androgen receptor inhibitors, in contrast, target the 'off' form of the protein, which, in the context of prostate cancer, can select for constitutively active, drug-resistant mutations.

"It's a different way to think about drugging proteins, certainly transcription factors," says Flare's co-founder and CSO Robert Sims. "It's not just, you know, a new site. It's actually a different structure. Even though it's still the same protein, it's in a different conformation." Flare's approach, which it calls 'pocket mapping', combines genetic insights into protein structure and function with structural biology. It conducts high-throughput covalent drug screens in whole cells to ensure that any binding events it identifies are physiologically relevant.

Quantro Therapeutics of Vienna is one of several firms targeting MYC, a transcription factor key to cellular growth and differentiation but also linked with myriad cancers when dysregulated. The company has studied MYC binding through an assay developed by its scientific founders, Stefan Ameres, of the University of Vienna, and Johannes Zuber, of the Institute of Molecular Pathology in Vienna. Newly transcribed RNAs in live cells are labeled by exposing them to 4-thiouridine, an analog of uridine. This alters the base pairing affinity of the putative uridines in the resulting transcripts from adenine to guanine, which subsequently results in thymidine-to-cytosine conversions during standard cDNA library preparation protocols prior to sequencing. Only genes that are actively undergoing transcription will exhibit these changes. Within 1–2 hours, Quantro's method – called QUANTROseq – detects perturbations to gene expression, proving far more sensitive to gene expression changes than RNA sequencing or tracking the expression of reporter genes.

Quantro's efforts at drugging MYC are still early stage. The company is taking multiple approaches to the task, and it is drawing on the hit identification capabilities of Hamburg, Germany-based Evotec, a seed investor in the company.

Many have tried – and failed – to target MYC over the years. Quantro's CEO Michael Bauer says that the QUANTROseq assay has shown that some molecules billed as MYC inhibitors actually have an indirect effect on the target. But Laura Soucek, of Vall d'Hebron Institute of Oncology and the Autonomous University of Barcelona, and colleagues have pioneered an approach to targeting MYC directly by disrupting its formation of a DNA-binding dimer with MAX protein. Their work spurred the formation of two Barcelona-based firms, Peptomyc and IDP Pharma, which have ongoing clinical programs (Table 1). Peptomyc has reported that its drug candidate, OMO-103, had a positive safety profile and showed preliminary evidence of activity in a first-in-human trial in heavily pretreated patients with a range of metastatic solid tumors.

Ten63 Therapeutics has also selected MYC-driven cancers for its lead program. The protein, says CEO and co-founder Marcel Frenkel, has several features that make it "very difficult" to target. It does not persist for long and is intrinsically disordered unless bound to its partner MAX; it is "exceptionally charged" in the region that binds DNA; and, because its function is to interact with other large macromolecules, it has large, flat recognition motifs rather than the deep binding pockets that drug hunters prefer. The company is based on the work of scientific founder Bruce Donald of Duke University, who developed a computational platform, called BEYOND, that combines physics and machine learning to explore the interactions between over 100 trillion (10^{14}) drug-like compounds and cryptic pockets hidden within transcription factor targets. It simplifies the search by focusing

News in brief

Cell-grown pork fat approved

San Francisco startup Mission Barns in September began selling its cultured pork fat to diners at local restaurant Fiorella after receiving regulatory approvals earlier this year. The company joins a small handful of companies selling cultured, or cell-cultivated, meat products and is the first to receive regulatory approval for animal fat.

Mission Barns grows belly fat cells from a US breed of Yorkshire pigs in proprietary bioreactors and mixes it with plant-based proteins to form meatball and bacon alternatives. The addition of the fat boosts the flavor and juiciness of the food, making it more like animal-based meat, but without harming animals. The US Food and Drug Administration approved the fat in March, and the US Department of Agriculture gave its green light in July. Sprouts Farmers Market will begin selling the food in the coming months, according to Mission Barns.

Lab-grown meat first entered the market in 2020, when Good Meat, a division of Eat Just from Alameda, California, served its cell-based chicken to club-goers in Singapore. The United States later followed by approving the company's chicken, along with cultured salmon from Wildtype in San Francisco, and cultured chicken from Upside Foods in Berkeley, California. Aleph Farms in Rehovot sells cell-based steak in Israel, and Sydney-based Vow in June received approval to sell cultivated quail in Australia. In addition to Mission Barns, other companies developing cell-based animal fat include Hoxton Farms in London, student-founded Genuine Taste in Toronto, and Mosa Meat in Maastricht, the Netherlands.

But cultured meat has faced political opposition backed by the livestock industry. Several US states have banned it to varying degrees. Texas passed a law in June banning the sale of cultured meat for two years – a rule that went into effect September 1. In doing so, the state joined Florida, Alabama, Nebraska, Montana, Indiana and Mississippi, which have also passed legislation against it.

on low-energy, stable conformations that are most likely to yield physiologically relevant results. In its MYC program, the company is progressing several different chemical series. The most advanced is in lead optimization.

Across the industry, most programs targeting transcription factors are either preclinical or in early clinical development. Efficacy data remain sparse, but in June at the 2025 American Society for Clinical Oncology meeting, Sapience Therapeutics reported promising, albeit preliminary, clinical data in glioblastoma, a condition that has long been a drug development graveyard. Its drug candidate, lucicebtide, is a first-in-class inhibitor of CCAAT/enhancer binding protein-β (C/EBPβ), a transcription factor that regulates genes associated with the immune response, adipogenesis (the formation of fat-storing adipocytes), gluconeogenesis (the synthesis of glucose from non-carbohydrate metabolites), liver regeneration and blood cell development.

Malignant cells in glioblastoma exist in four different cellular states, depending on the molecular cues they receive. C/EBPβ is a key regulator responsible for pushing brain tumor cells toward one of them, along a differentiation pathway that leads to a mesenchymal phenotype. This results in a more aggressive disease course and the emergence of resistance to current treatment. "So blocking that transition, we believe, is one of the reasons why we're seeing the results," says Sapience founder and CEO Barry Kappel. Lucicebtide is a peptide solely composed of D-amino acids, so it avoids the rapid, protease-mediated degradation that conventional L-amino acid-based peptides undergo. Its structure includes what the company calls a 'cell entry motif' – a short stretch of amino acids that promotes cellular uptake – which can be tuned to favor cytoplasmic or nuclear delivery, as required.

The testing of the investigational agent in a small-scale, ongoing phase clinical 1/2 trial suggests there could be survival benefits. Although Sapience's open-label study did not have a control arm, six of nine patients with newly diagnosed disease achieved progression-free survival and overall survival extending well beyond that of historical controls. Given the small number of patients involved, these initial observations do not comprise clearcut evidence of efficacy as yet, but the company is now drawing up plans for a randomized trial in a larger number of patients.

Unravelling the biology of many transcription factors and figuring out how to target them remains a work in progress. "It's really important to understand the regulatory networks of transcription factors – to know what are the interaction partners, what are the co-factors, how are transcription factors regulated," says Joachim Rudolph, senior fellow, discovery chemistry, at Genentech. The field still has plenty of what Kappel calls "white space." Of the estimated 20,000 members of the human proteome, only about 5% have been drugged. Not every protein – and not every transcription factor – will be an appropriate drug target, of course. The full extent of the druggable proteome is not yet apparent. What is becoming increasingly clear, however, is that the 'undruggable proteome' is steadily shrinking. Over time, the term will become obsolete.

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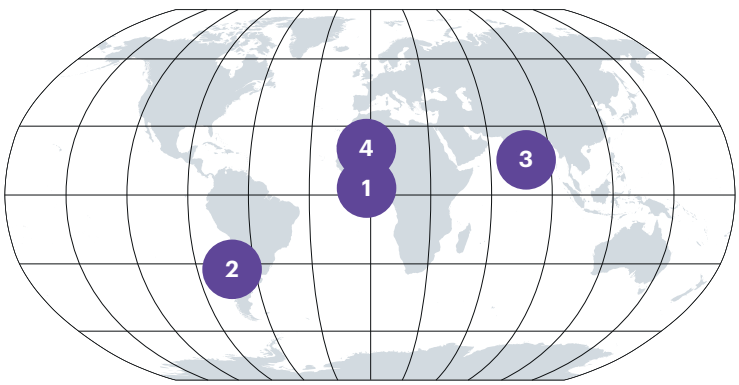
Biotech news from around the world

1. GHANA
Accra-based Yemaachi Biotech wants to sequence 15,000 cancer genomes from African patients over the next three years through the African Cancer Atlas (TACA), a consortium that includes over 25 hospitals and research institutions across 9 African countries. People of African descent are under-represented in genomic datasets that underpin cancer diagnosis, treatment and drug development globally – they account for less than 2%, as compared with nearly 80% from North American and European ancestry. Yemaachi has recruited Roche as its first anchor partner in TACA.

2. CHILE
Agbiotech startup Neocrop Technologies has developed a high-fiber wheat in partnership with seed companies Campex Baer and Argentina's Buck Semillas. Chile's agricultural regulator confirms that the new wheat line, developed with CRISPR technology, will not be classified as a GMO, clearing the way for field trials without further regulatory barriers and making it the first gene-edited wheat in the Americas to receive such a go-ahead. The wheat line has a dietary fiber content up to ten times higher than conventional flour wheat without compromising the flavor and texture of its white flour.

3. INDIA
The Biofoundry Network launches with 21 facilities across the country to help accelerate biomanufacturing, reduce dependence on imports, foster startup growth and create jobs for India's bioeconomy. The biofoundry facilities will act as shared infrastructure for startups, small and medium-sized enterprises, and academic institutions.



4. BURKINA FASO
The government of Burkina Faso suspends all activity by Target Malaria almost two weeks after the non-profit research consortium released about 16,000 GMO mosquitoes as part of a gene drive project to rid the country of malaria. Target Malaria has worked in the country since 2012 but recently became a target of a disinformation campaign on social media that aims to sow distrust of Western countries and organizations. The military junta in charge of the country has emphasized national autonomy, revoking the licenses of other foreign non-governmental organizations.