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BioCentury's 2021 class of emerging companies

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The class of innovators in BioCentury's 2021 Emerging Company Profiles showcases evolving approaches to overcoming the challenges of new modalities.

The collection, which includes 118 start-ups, focuses on private biopharmas developing novel platforms or building first-in-class or best-in-class pipelines, that typically have emerged from stealth or raised their first venture rounds in the past three years. The series represents a curated group of companies with compelling science, rather than a comprehensive collection of newcos.

Last year's ECPs display continued enhancements in protein degrader technology, the latest crop of RNA therapeutics, strategies to improve delivery of RNA and DNA therapies, and techniques to regulate endogenous gene expression.

Protein degradation start-ups are advancing the field in different directions. Some are avoiding E3 ligase resistance mechanisms by developing compounds that recruit multiple ligases, or creating degraders independent of the E3 ligase pathway. Others are exploiting cellular waste systems beyond the proteasome.

The newest crop of RNA companies indicates the field is expanding its focus on circular and self-amplifying RNA, which provide longer-lasting doses than conventional mRNA, among other advantages.

A handful of emerging companies are modifying oligonucleotide therapies to enhance delivery to tissue types such as CNS and muscle.

Several gene therapy newcos are addressing the safety and efficacy issues that brought a year of setbacks in 2021, through viral vector engineering and non-viral vector approaches.

A trio of gene editing companies is looking to bypass safety issues of permanent double-stranded DNA changes by modifying DNA in other ways, such as tinkering with epigenetics.

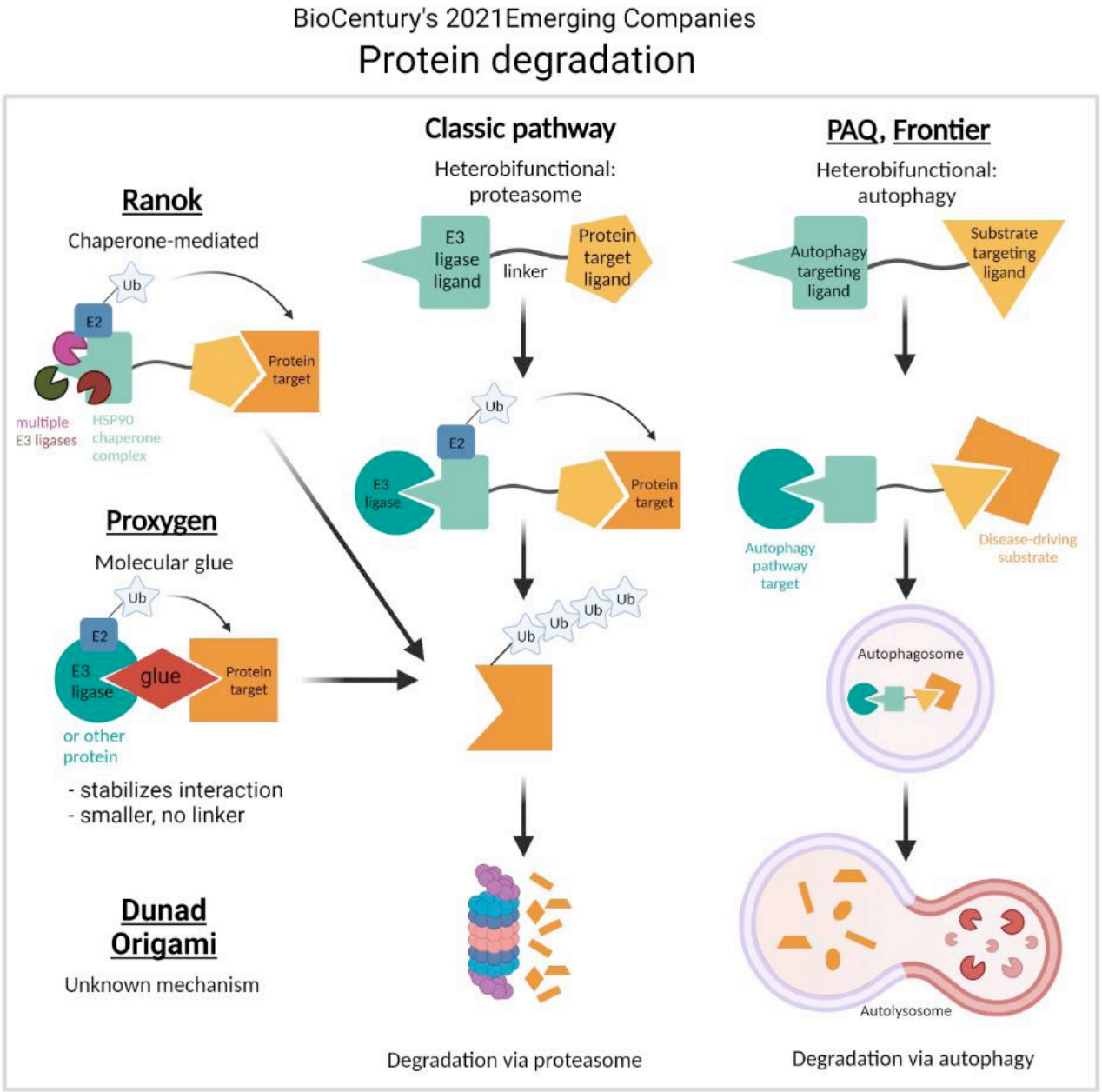
The many forms of protein degraders

Momentum continues for targeted protein degradation companies, with half a dozen featured in the 2021 emerging company series — three in cancer, two in neurology and one in both.

The "classic" targeting chimera (TAC) degrader is a heterobifunctional structure that uses a linker to connect separate ligands against a target of interest and an E3 ligase, which ubiquitinates the target and sends it to the proteasome for degradation.

All six of the emerging companies are moving beyond the classic construct, and they're doing it in six different ways, from making smaller degraders to enabling degradation of larger substrates to pioneering selective delivery to tumor cells.

Austria-based Proxygen GmbH, whose screening platform grew out of work at the Austrian Academy of Sciences, joins a small group of companies seeking to identify molecular glues, small molecules that can bind both a target protein and an E3 ligase without the need for separate ligands and a linker.



Protein degradation newcos
BioCentury's 2021 emerging companies

Company	Description	Therapeutic focus
Frontier Medicines	Chemoproteomics platform to discover small molecules and protein degraders for difficult-to-drug targets	Cancer
Proxygen	Screening platforms to identify molecular glues for targeted protein degradation	Cancer
Ranok	Chaperone-mediated targeted protein degradation	Cancer
Dunad	Monovalent protein degradation platform	Neurology, cancer
Origami	Protein degrader and corrector platform	Neurology
PAQ	Autophagosome-tethering compound (ATTEC) platform	Neurology

Dunad Therapeutics Ltd., which spun out of the University of Toronto in 2020 and is headquartered in in the U.K., is degrading targets through a pathway that's independent of the E3 ligases. The company has said its molecules are neither heterobifunctional constructs nor molecular glues, but has not disclosed details.

Novartis AG (SIX:NOVN; NYSE:NVS) gained access to Dunad's platform in November for $24 million in an upfront payment and equity investment. The biotech is eligible for $1.3 billion in discovery, development, regulatory and sales-based milestones, plus royalty payments.

Degraders can also use other cellular waste systems beyond the proteasome, such as autophagosomes, to target a broader array of disease-causing substrates including protein aggregates, pathogens, lipids and organelles. Cambridge, Mass.-based PAQ Therapeutics Inc., which raised a $30 million series A round led by Sherpa Partners in July, is designing autophagosome-tethering compounds (ATTECs) in which one part of the molecule binds a component of the autophagy pathway and another binds a disease-causing substrate.

Fellow newco Frontier Medicines Corp. also is developing compounds that trigger the autophagy pathway. Frontier's approach, based on chemoproteomics technology developed at University of California Berkeley, uses covalent ligands in cell line-based screens to identify transient binding sites on hard-to-drug proteins, including sites that are only exposed in disease-specific contexts. These hits then serve as the basis for developing ligands to incorporate into heterobifunctional compounds, dubbed AutoTACs, that tag targets for degradation. In a partnership with AbbVie Inc. (NYSE:ABBV), Frontier is identifying ligands that target novel E3 ligases and undisclosed cancer and immunology targets.

Origami Therapeutics Inc.'s platform, ORICISION, enables discovery of small molecule protein degraders or protein conformation correctors to counteract protein misfolding. The company determines the right type of therapy for a given neurodegenerative disease using patient-derived disease models. The San Diego, Calif.-based newco's lead program, ORI-113, is in the degrader category, selectively reducing mutant HTT protein to treat Huntington's disease. CEO Beth Hoffman told BioCentury in October that the company hadn't yet identified the cellular waste system the molecule induces for HTT degradation.

Ranok Therapeutics Co. Ltd., headquartered in Hangzhou, China, is taking a chaperone-based approach to achieve tumor-specific protein degradation. Instead of binding directly to an E3 ligase, Ranok's molecules, dubbed CHAMPs, bring a target molecule to a HSP90 chaperone complex that includes multiple E3 ligases. The method takes advantage of the fact that HSP90 is highly activated in tumor tissues to achieve a higher therapeutic index than classic degraders, potentially offering a dosing advantage. The therapeutics may also be able to overcome resistance mechanisms associated with E3 ligase mutations because the complex includes more than one E3 ligase.

RNA of all kinds

In January, buysiders and bankers interviewed by BioCentury flagged oligonucleotides as therapeutic modalities that could have a big year. Growing interest in oligonucleotides follows the December approval of siRNA therapy Leqvio inclisiran

from Novartis and partner Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY), which marked the entry of the modality into a prevalent indication.

Last year's class of emerging companies highlights the next frontiers in RNA-based therapies, including circular RNA, self-amplifying RNA and tRNA.

While most research on circular RNAs has focused on their use as biomarkers or drug targets, two start-ups on the list, Laronde Inc. and Orna Therapeutics Inc., are developing circular RNAs as therapeutic platforms. Circular RNA achieves longer-lasting expression than linear mRNA and could be easier to manufacture.

Orna, which emerged from stealth in February with an $100 million including an $80 series A round led by MPM and Taiho Ventures, packages circular RNAs in lipid nanoparticles that home to different cell types, enabling, for example, in vivo engineering of immune cells to create CAR-expressing immune cells. The strategy bypasses manufacturing steps such as ex vivo manipulation of autologous or allogeneic cells that are bottlenecks for cell and gene therapies.

The basis of Laronde's platform is the ability of some long non-coding RNAs to naturally form circles that are non-immunogenic and enable longer-lasting therapeutic protein production than conventional mRNA — on the order of a week or more instead of two to three days. Laronde raised a $50 million series A round from Flagship Pioneering in May, then followed up in August with a $440 million series B that included Flagship, T. Rowe Price, Invus, CPP Investments, Fidelity, funds and accounts managed by BlackRock, and Federated Hermes Kaufmann Funds.

Circular RNA manufacturing could be cheaper than for linear RNA because it involves fewer steps and modifications; circular constructs don't require mRNA caps or tails, for example.

Like circular RNA, self-amplifying RNA also provides longer-lasting doses than conventional mRNA, but stands out for its ability to evoke strong antibody and cytotoxic T cell responses, which is useful for creating vaccines. At least four self-amplifying RNA vaccines are in clinical development for COVID-19.

Replicate Bioscience Inc., which raised a $40 million series A round in September from founding investor Apple Tree Partners, is taking the technology beyond prophylactic vaccines into cancer immunotherapy. Replicate's oncology platform, termed synthetic immune lethality, directs the immune system to target acquired resistance mutations as foreign, forcing the cancer cell to either remain susceptible to a targeted therapeutic or mutate and be targeted by the immune system. The company's lead program, RBI-1000, is in development for breast cancer patients resistant to endocrine therapy.

Replicate's platform includes a suite of synthetically derived alphavirus vectors that have characteristics suited to different types of transgenes. The company is using an in vivo screening platform to test combinations of different encoded proteins

RNA innovators

BioCentury's 2021 emerging companies

Company	Description	Therapeutic focus
Circular RNA		
Laronde	Modular, programmable circular RNA platform to deliver therapeutics	Cancer, cardiovascular, dermatology, endocrine/metabolic, hematology, inflammation, musculoskeletal, neurology, ophthalmology
Orna	Circular RNA therapies delivered in nanoparticles	Cancer, genetic disease
Self-amplifying RNA		
Replicate	Self-replicating RNA platform with synthetically derived alphavirus vectors	Autoimmune, cancer, inflammation
tRNA		
Alltrna	tRNA therapeutics	Undisclosed

and formulations to find the optimal fit for self-replicating RNA therapeutics.

Flagship Pioneering continues to place bets on RNA platforms. In addition to launching mRNA play Moderna Inc. (NASDAQ:MRNA) and circular RNA company Laronde, Flagship incubated tRNA therapy pioneer Alltrna in 2018, publicly launching the company in 2021.

The job of tRNA, or transfer RNA, is to decode the mRNA sequence for protein synthesis. After the mRNA is created in transcription, specific tRNAs identify the amino acids that correspond to each three-nucleotide mRNA codon, then transfer the amino acid to the growing polypeptide chain.

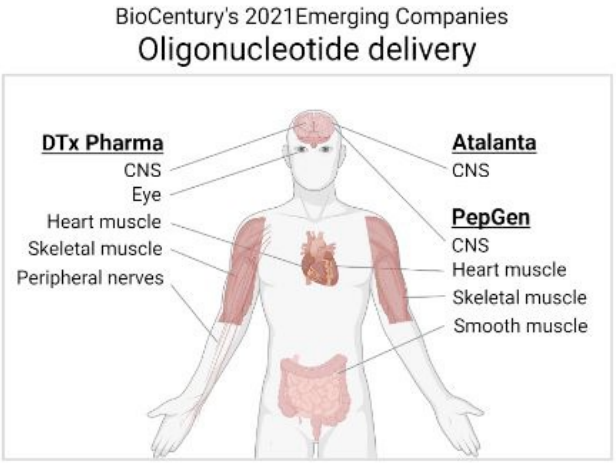
One application of Alltrna's technology is engineering tRNA molecules with new sequences or modifications that can render them capable of correcting mutations. For example, if a patient has a mutation that causes a premature stop codon or an incorrect amino acid to be added to the chain, Alltrna can create an engineered tRNA that recognizes the mutant codon but adds the correct amino acid instead. The company hasn't yet disclosed indications.

Improving oligo delivery

Reaching extrahepatic targets has been a challenge for systemically delivered RNA therapeutics, and intrathecal delivery does not reach the entire brain, limiting the technology's use as CNS therapeutics. A growing number of newcos aim to solve these problems, improving delivery to a wide variety of tissue types.

The University of Massachusetts Medical School spinout Atalanta Therapeutics Inc. is developing branched oligos, which consist of two or more chemically modified siRNA molecules joined by a linker. The company generated much interest when it demonstrated in Nature Biotechnology that its branched siRNAs enabled durable, widespread gene knockdown throughout the CNS of mice and non-human primates, including hard-to-reach deep brain tissues such as the striatum. Atalanta emerged from stealth in January 2021 with $110 million in total funding, comprising a series A from F-Prime Capital and upfront payments from two partners: Biogen Inc. (NASDAQ:BIIB) and the Genentech Inc. unit of Roche (SIX:ROG; OTCQX:RHHBY).

PepGen Inc. spun out of the University of Oxford to develop its Enhanced Delivery Oligonucleotide (EDO) platform that contains cell-penetrating polyarginine sequences that stabilize oligonucleotide therapies and increase the number of molecules that reach target cells. PepGen's candidates have broad distribution to muscle tissues including skeletal, heart, diaphragm and smooth muscle as well as the CNS. Its lead candidate EDO51 targets exon 51, a validated genetic target



relevant to about 13% of Duchenne muscular dystrophy patients.

San Diego, Calif.-based DTx Pharma Inc. is using fatty acid ligands to overcome delivery challenges for RNA therapies, starting with siRNAs. The fatty acid-conjugated siRNAs bind albumin in circulation, which protects them, and enter cells via fatty acid receptors on cell membranes. The company's most advanced compound is designed to treat pan retinitis pigmentosa; it's also exploring muscle, heart and CNS disorders.

More established RNA companies are also making moves into new delivery methods. For example, in July, antisense pioneer Ionis exercised its option to license from Bicycle Therapeutics plc (NASDAQ:BCYC) tissue-targeted delivery vehicles that use a TFR1-binding bicyclic peptide to target muscle tissues and the CNS.

PYC Therapeutics Ltd. (ASX:PYC; FSE:PH7), which is using its peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO) technology to deliver RNA therapeutics to the eye and CNS, reported last year that the platform achieved delivery throughout the brains of mice given intracerebroventricular RNA injections of an antisense RNA targeting SMN exon 7.

Gene therapy, targeted

Adeno-associated viral (AAV) vectors have been the vector class of choice for in vivo delivery because they're much less likely to integrate into the host genome than lentiviral vectors — and are therefore theoretically less likely to cause insertional mutagenesis and cancer.

Selectively targeting tissues outside the liver has been a challenge, however, as has the vectors' limited carrying

Vector innovations for gene engineering

BioCentury's 2021 emerging companies

Company	Description	Therapeutic focus
AAV		
AviadoBio	Precision delivery of gene therapies for CNS disorders	Neurology
Capsida	Gene therapies with engineered AAV vectors and genetic cargo	Neurology
Lentiviral		
Genespire	Gene editing platform and immune-shielded lentiviral vectors	Endocrine/metabolic, hematology
Adenoviral		
Ensoma	Engineered adenoviral vectors lacking viral genomic material for in vivo cell and gene therapies	Autoimmune, cancer, hematology, infectious
Non-viral		
Anjarium	Non-viral gene therapies	Undisclosed
Code Bio	Non-viral gene therapies for genetic diseases	Endocrine/metabolic, musculoskeletal
Intergalactic	Non-viral gene therapies	Cancer, ophthalmic, pulmonary

capacity and their propensity to trigger an immune response that prevents redosing and leads to inflammatory toxicities.

To improve tissue distribution, London, U.K.-based AviadoBio Ltd. is taking a neuroanatomy-based approach, directly injecting AAV vectors to well-connected "neural hubs" within the CNS such as the thalamus, a brain region that projects to much of the cerebral cortex, to treat diseases such as frontotemporal dementia and amyotrophic lateral sclerosis. The start-up, which raised a $80 million series A in December co-led by NEA and Monograph Capital, is aiming to begin first-in-human testing of its FTD program by year-end. The therapy delivers the PGRN gene and is in development for FTD patients with PGRN mutations.

California-based Capsida Biotherapeutics Inc., which launched in April with a $50 million series A round from Versant Ventures and Westlake Village BioPartners, is one of over a dozen companies working on capsid engineering to improve a range of properties. The newco is using a capsid selection method called Cre-recombination-based AAV targeted evolution (CREATE) that identifies capsid variants with tropism to specific tissues. By applying AI and machine learning, the company can create billions of capsids to screen in 2-3 weeks. Using the tech, Capsida has identified an AAV that can transduce 70% of neurons in mice, cross the blood-brain barrier, and avoid the liver to reduce toxicity.

Milan-based Genespire s.r.l., a spinout of San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), is among the handful of companies still developing lentiviral vectors for in vivo use, with immune-shielded technology designed to boost efficacy. The platform prevents vector phagocytosis by using a production cell line that overexpresses CD47, elevating viral surface density of the "don't eat me" signal. The transgene expression cassette also includes regulatory elements to restrict expression to liver cells, and microRNAs specific for hematopoietic lineage cells to block off-target expression in antigen-presenting cells in the liver and spleen — a strategy to prevent immunity against the therapy.

Boston-headquartered Ensoma, which launched in February 2021 with a $70 million series A round and a Takeda deal in hand, is overcoming limits to cargo size with engineered genome-free adenoviral vectors that can carry up to 35 kb of cargo, versus less than 5 kb for AAVs. The technology can modify hematopoietic stem cells (HSCs) to express, edit or regulate a gene, or to turn HSC-derived cells into engineered immunotherapies such as CAR T cells.

Turning away from viral vectors, Switzerland-based Anjarium Biosciences AG is using lipid nanoparticles that can house payloads larger than a typical viral vector can carry, while employing extracellular vesicles to reach target tissues.

One concern among non-viral delivery methods is a lower gene transfer efficiency. Code Biotherapeutics Inc. and Intergalactic Therapeutics Inc. are developing synthetic DNA constructs that improve transfer efficiency by designing regulatory control elements into the plasmids, and avoid immunogenicity by removing pathogenic sequences. Hatfield, Pa.-based Code spun out of Philadelphia-area tools and diagnostics company Genisphere LLC in April 2020. Intergalactic Therapeutics Inc. was founded by ex-Biogen EVP Michael Ehlers in 2020 and backed by a $75 million tranched series A round from Apple Tree Partners.

Gene modifications, hold the breaks

Excitement for gene editing therapies hit a high last year when Intellia Therapeutics Inc. (NASDAQ:NTLA) and partner Regeneron Pharmaceuticals Inc. (NASDAQ:REGN) presented the first clinical data for a systemically delivered CRISPR-based gene editing therapy, showing a single dose of NTLA-2001 reduced serum TTR levels in patients with hereditary transthyretin amyloidosis with polyneuropathy.

Off-target edits remain a major concern, however, as the tech could cause permanent, unwanted double-stranded DNA changes. Three newcos in BioCentury's 2021 emerging companies are sidestepping the safety issue.

Instead of making double-stranded DNA breaks and plugging new nucleic acids into the hole like CRISPR-Cas9, Cambridge, Mass.-based Prime Medicine Inc. is pioneering prime editing – which rewrites the DNA sequence without making cuts. It uses a Cas9 nickase — an enzyme that nicks a single strand of DNA instead of making a double-stranded break, making possible a range of genetic corrections including point mutations and insertions. Prime was founded in 2019 with a $100 million series A round, then publicly launched last year with $215 million in a crossover-laden series B.

Chroma Medicine Inc. and Tune Therapeutics Inc. are both leveraging endogenous epigenetic mechanisms to control gene expression via epigenetic editors that create marks to either repress or activate the expression of specific genes.

Epigenetic editors can also address diseases that require multiple genes to be turned on or off, which may be more difficult for genomic editing platforms given the inherent safety risks. None of the three companies have disclosed a therapeutic focus.

Cambridge, Mass.-based Chroma debuted in November with a Cormorant-led $125 million A round, and Seattle, Wash.-based Tune launched in December with a $40 million funding co-led by New Enterprise Associates and Emerson Collective.

Cell therapies were also featured among BioCentury's 2021 Emerging Company Profiles. A second installment of the ECP round up will delve into the companies' cutting edge approaches to cell therapy creation.

Gene modification newcos
BioCentury's 2021 emerging companies

Company	Description	Therapeutic focus
Genome		
Prime Medicine	Prime editing to correct genetic mutations and make genetic changes	Undisclosed
Epigenome		
Chroma Medicine	Epigenetic editors to control gene expression	Undisclosed
Tune Therapeutics	Epigenetic editing platform	Undisclosed

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