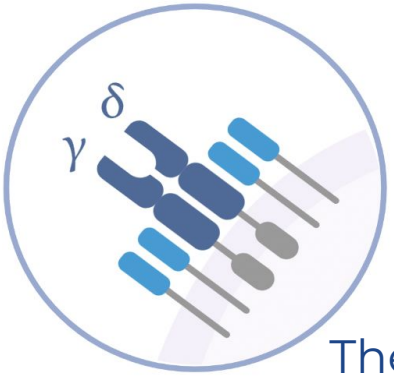


Ambrosia Therapeutics

The future of solid tumour treatment and beyond

BUSINESS PLAN

Stephanie George, Katerina Ovchinnikova, Blanca Marin

Healthcare Need

CAR-T treatments have been licensed for the treatment of liquid tumors, which account for 10% of all cancers, but they have yet to revolutionize the therapy landscape for solid tumors. Solid tumors, which account for 90% of all malignancies, continue to have a high unmet need and there are limitations to current available treatments (Figure 1).

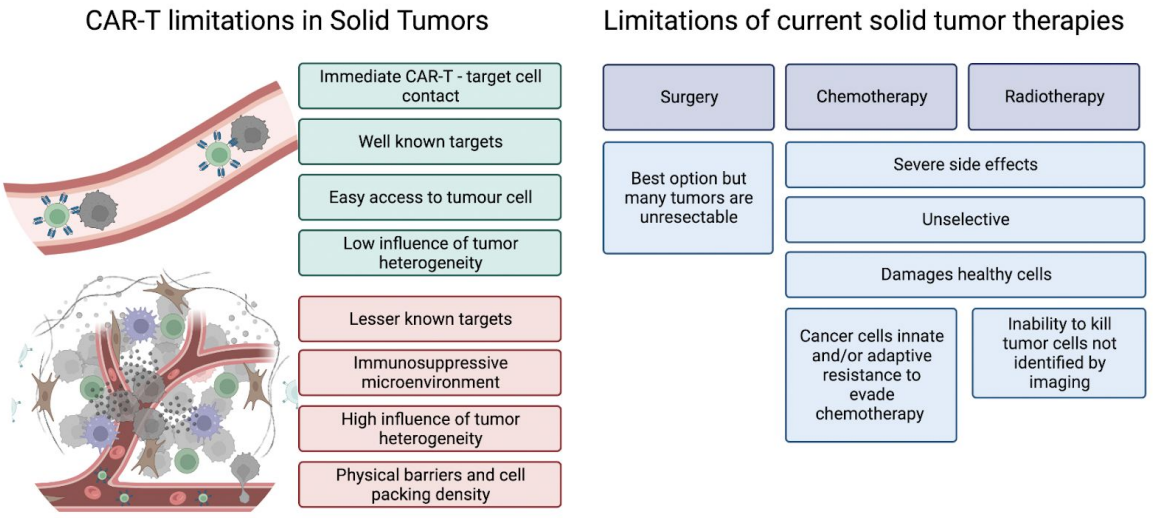


Figure 1: Limitations of CAR-T in solid tumors and current solid tumor therapies

Cancer therapies pose a large economic and societal impact on the U.K, with an annual cost of over £5 billion (Gov.UK, 2015). Cell and Gene Therapies are a promising cancer treatment, but as the majority of these therapies are autologous in nature, their costs are economically unfavorable, costing, on average at least $1.5 million (Owens, 2022).

The difficulty of CAR-T to infiltrate solid tumors, as well as the complex and costly customized manufacturing process that needs patient-derived (autologous) cells, are the two primary barriers to its use. γδT cells are known to mediate natural anti-tumor responses (may infiltrate the solid tumor), and they lack allergenicity, allowing for batch manufacturing. This significantly reduces costs compared to autologous cell development (Harrison et al., 2019).

Proposed Solution

Senescent cells are characterized by the cessation of cell division and have been recognised as an emerging cancer hallmark (Hanahan, 2022). Senescent cells resemble cancer cells in phenotype, because they are "self" cells, the immune system is unable to identify them. Their development of a senescence-associated secretory phenotype (SASP) transforms them into proinflammatory cells capable of promoting tumor growth. Furthermore, aging and senescence substantially modify the tumor microenvironment (TME), favoring the formation of immunosuppressive cells that promote treatment resistance and immune evasion. Senescent cells may be selectively and effectively removed by senescent-targeted clearance, offering a novel approach to the therapy of solid tumors.

Our team hopes to utilize γδ T cells as a platform technology with dual specificity for a senescent target and a cancer target.

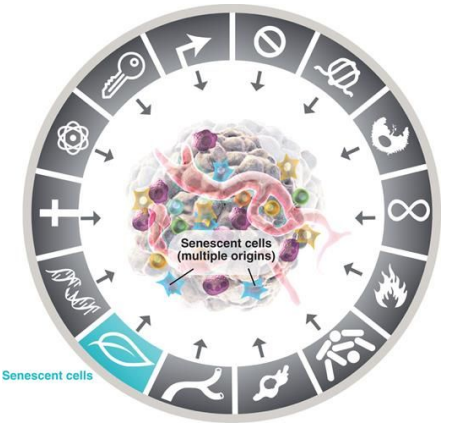


Figure 2: Senescent cells are an emerging hallmark of cancer (Hanahan, 2022)

Proposed Solution

The aim of the solution is to target senescent cells to inhibit tumor formation (Figure 3).

1. Senescent cells accumulate in the tumor microenvironment
2. By targeting them, the solution mitigates cancer cells ability to evade treatment by infiltrating the tumor with their target
3. Clearing senescent inhibits SASP-related chronic inflammation

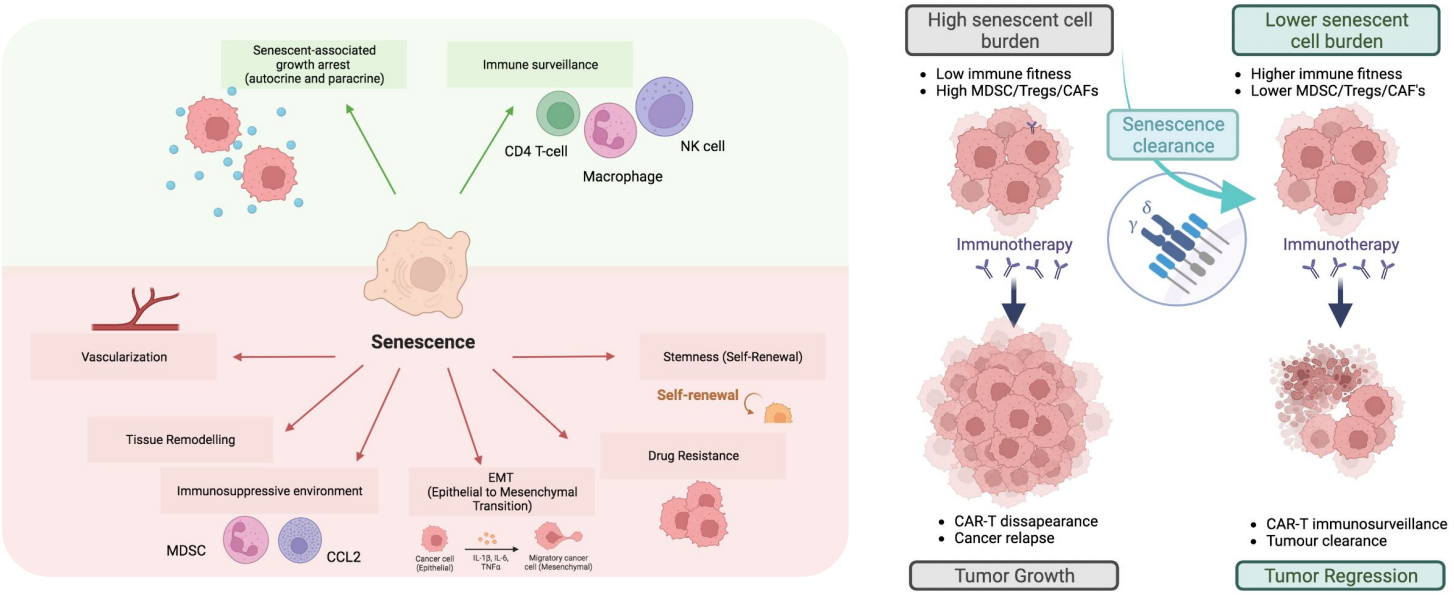


Figure 3: Model of senescence-targeted clearance (Zeng et al., 2018)

The ability to characterize cancer patients based on the elevation of certain markers has revolutionized the diagnostic and therapeutic landscape. The increasing use of tools such as liquid biopsy allows for detection of markers to selectively target with immunotherapies (Nikanjam, Kato and Kurzrock, 2022). Biomarker advancements generating momentum in precision medicine have resulted in the development of biomarker-guided studies such as basket trials, in which a targeted immunotherapy is assessed for numerous malignancies that share common markers. Initially we plan to focus on one selected dual γδ T senescence target and cancer target. Our long-term vision is a platform technology, enabling novel senescence targeting coupled with an array of cancer markers, the therapeutic pathway of the platform is the following:

Tumor cancer biomarker test	**Identify cancer targets and senescent phenotype**	Co-Stimulatory CAR expressing γδ T cells with personalized markers
Biopsy test of patient tumour	Identification of optimal cancer biomarker and senescent cell identified for the patient	Using γδ T cell platform, targeted therapy produced

The urokinase-type plasminogen activator receptor (uPAR) is a marker of senescence and expressed across a number of cancers (figure 4), proving to be a prognostic marker with high levels indicating poor survival. A number of malignancies have elevated uPAR expression during inflammation and tissue remodeling (Smith and Marshall, 2010), including bladder cancer, breast cancer, lung cancer, ovarian cancer, head and neck cancer, and cervical cancer (appendix 10). Sustained elevated uPAR expression has been linked to cancer cell proliferation and metastasis (Degryse et al., 2017). In tumor-promoting interactions, several cancer biomarkers, such as insulin-like growth factor receptor 1 (IGF1R), have a direct link with uPAR (Huber et al., 2016; Zhai et al., 2022). Our technology is a platform technology that utilizes the emerging hallmark of cancer (senescence) with a novel dual recognition and activation method utilizing targets implicated with uPAR (Appendix 1). This results in modified γδ T cells with optimum anti-tumor impact.

To investigate potential targets, we analyzed mRNA expression across cancers reported in the cancer genome atlas (Appendix 1).While the proposed solution is a platform which has the promise of targeting all solid tumors and can have even broader applications, we propose an initial trial based on uPAR and IGF1R co-overexpression across cancers. The study will follow a basket trial format, for which eligibility will be based on the presence of uPAR and IGF1R (confirmed by IHC), which we primarily identified as highly expressed in the following 6 cancers:

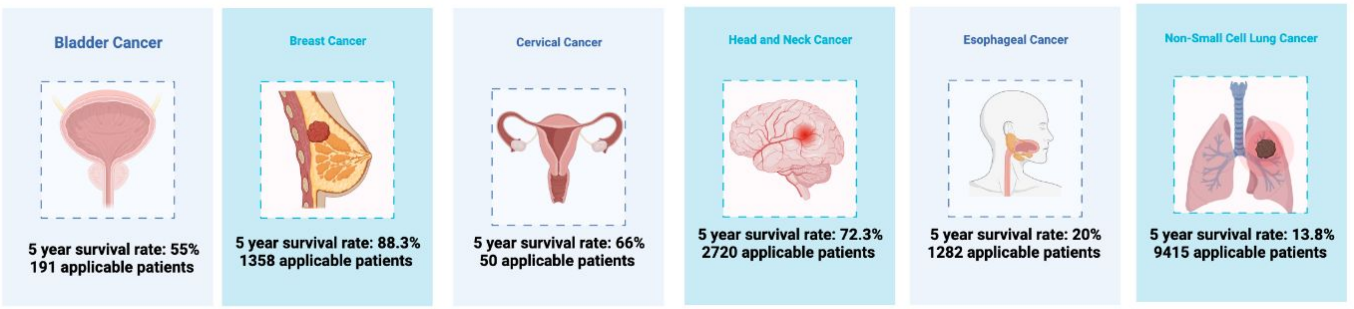


Figure 4: Cancers of focus, with 5 year survival rates (Gov.UK, 2021), and number of applicable patients as of 2022.

By utilizing γδ T cells, the proposed solution circumvents several challenges in cancer therapy, by recognizing and removing modified cells independent of their HLA-antigen presentation, making them novel and promising cells for cancer immunotherapy. Additionally, γδ T cells present the following benefits:

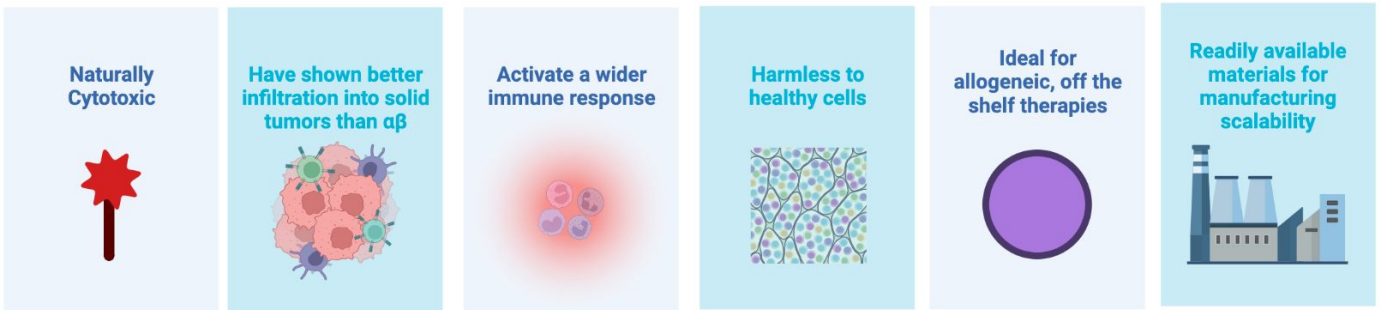


Figure 5: Benefits of γδ T cells

Competitive Advantage

The following five companies have been identified as competitors, either using γδ T cells, targeting scenescents or multi-targeted platforms. Ambrosia offers a competitive advantage by creating an allogeneic platform for targeting solid tumors, which is a main limitation of those competitors using CAR-T cells. By having a dual targeted approach, using scenescents, the therapy directly targets the cancer sight by being personalized to the cancer and patient.

Classification	Company	Product	Method	Stage	Limitations
γδ T cells for cancer therapy	TC Bipharm	OmnImmune	Unmodified allogeneic γδ T cells for Acute Myeloid Leukemia	Phase II/III	Does not target solid tumors
		OmnImmune	Undisclosed for solid and haematological tumors	Pre-clinical	Uncharacterised due to lack of information
Senescent cell targeting	StarkAge Therapeutics		Immunotherapies for idiopathic pulmonary fibrosis and other age-related diseases	Discovery	No indication of application to cancer therapy
	SIWA Therapeutics		Targeting PDAC with monoclonal antibody SIWA318H	Phase II	CAR-T therapy
Multi-targeted cell and gene therapies	Aurealis Therapeutics	AUP-55	Genetically modified bacteria expressing human therapeutic proteins	Pre-clinical	Only shows pre-clinical efficacy in ovarian cancer
	Elicera	iTANK	Multifunctional CAR-T platform inducing pro-inflammatory microenvironment and activating CD8+ killer T cells	Phase I/II	CAR-T therapy

Figure 6: Competitors, their products, methods, stage of development and limitations (TC Bipharm) (StarkAge) (SIWA Therapeutics) (Aurealis Therapeutics) (Elicera Therapeutics AB)

Freedom to Operate

The only applicable intellectual property which has been filed, awaiting approval is *Senolytic CAR-T cells targeting UPAR, a cell surface and secreted senescence biomarker* (Memorial Sloan Kettering Cancer Center, 2020) . This patent cites a CAR-T target for UPAR and in the instance that the patent is approved, the technology circumvents their claim due to the allogeneic γδ T CAR approach with dual targets, rather than CAR-T as shown in the patent.

Recent research has called into question whether CAR-T should be patentable as therapeutic, rather than a process, is justified. This viewpoint is supported by the fact that in the CAR-T procedure, T-cells are withdrawn from a patient, changed ex vivo to form CAR-T-cells, and then returned to the same patient. As a result, these procedures describe a way of treating each individual patient rather than producing a product for widespread sale and commercial usage. They should not be granted patent protection as goods or matter compositions, according to the reasoning. Since γδ T will be produced by donor derived cells in batches and differ mechanistically the process is patentable, and differs mechanistically with dual specificity.

Project Management

Our projected timelines and total cost per trial stage are presented in the Gantt chart (see **Figure 5**). The technology readiness level has been assessed along our clinical development pathway and presents likely sources of funding (**Appendix 6**). Investment required: £1.7M to reach phase II completion, this will have resulted in approximately 218 patients dosed (see **Figure 9**). Upon projected Phase III initiation in 2029, we anticipate either licensing deals which we estimate to be $6M, which is a conservative figure compared to our analysis of licensing agreements for adoptive cell therapies in 2022 (see **Appendix 4**).

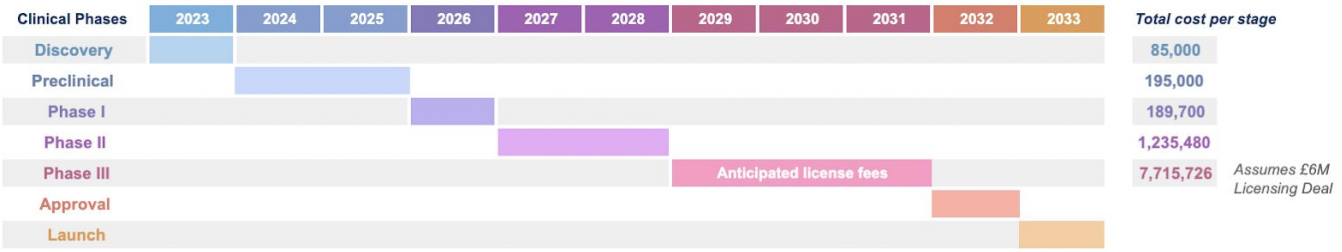


Figure 5: Gantt chart illustrating timelines and total cost per trial stage

Route to Market

Clinical Trials

Considering the product we are offering – a platform to target all solid tumours expressing high levels of UPAR and IGFR – we determined that the best design for our clinical trials would be a **basket trial**. This consists of evaluating a targeted therapy on multiple cancer types simultaneously, all which share common feature, in this case, UPAR and IGFR expression. This design methodology will allow us to identify the tumour types which respond best to our therapy, providing direction for future development (McNair, 2020). The patient inclusion and exclusion criteria for our trials are defined in **Figure 6**. A basket trial novel clinical trial design allows us to capture a broader market and treat a greater number of patients with severe unresectable tumors that harbor IGF1R and UPAR.

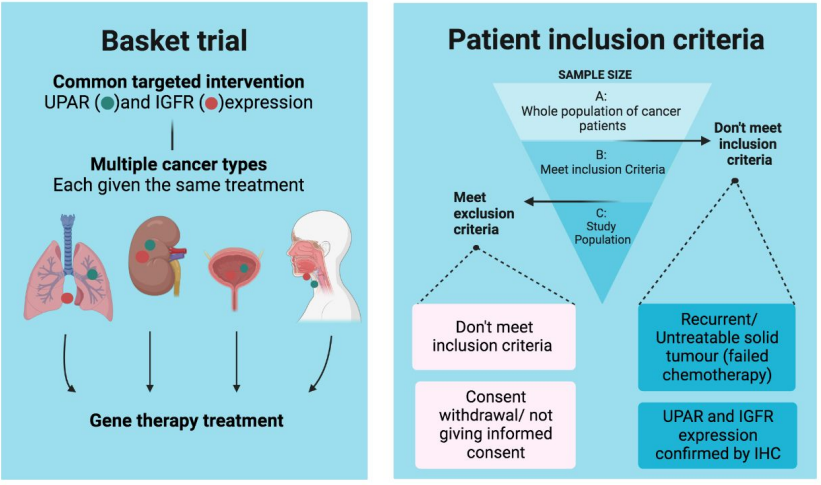


Figure 6: Basket clinical trial design and Patient inclusion/exclusion criteria for the trial

Commercial Scale Up

For the 6 cancers identified in our analysis of cancer genome atlas data (**Appendix 1**). Considering that immunotherapies are a third-line therapy, we have calculated the patient population at stage IV, both globally and in the UK and calculated the estimated number of patients with both UPAR and IGF1R markers (**Appendix 2 & 3**).

The total addressable market is calculated as the global cancer incidence at stage IV, and the estimated number of patients with both UPAR and IGF1R markers. whereas the total serviceable available market (SAM) is UK stage IV incidence with uPAR and IGF1R.

The annual growth of incidence rates from 2018 were used to forecast cancer incidence (**Appendix 3**). This equates to a TAM of 499,034 patients in 2033, and a SAM of 168,514 UK patients from product launch in 2032 to 2040, represented in the market size forecast (**Figure 7; Data: Appendix 3**).

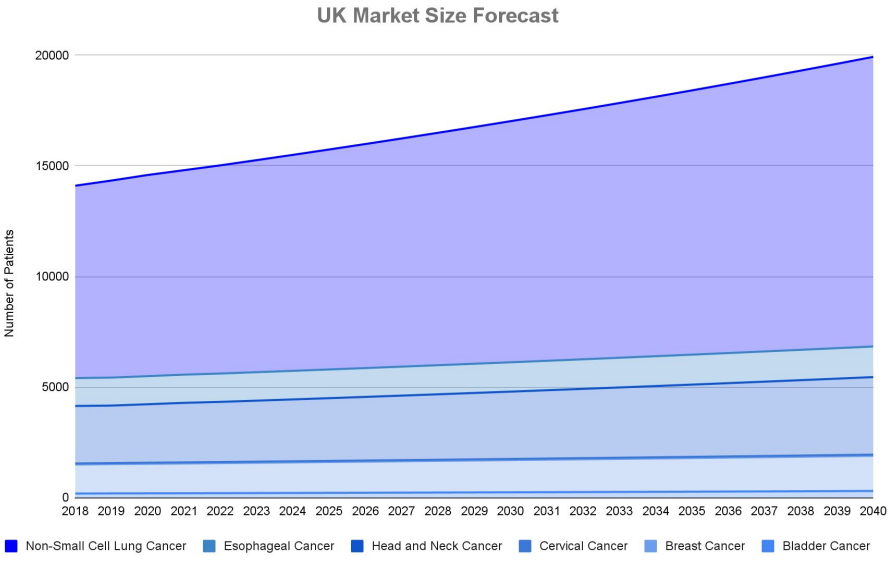
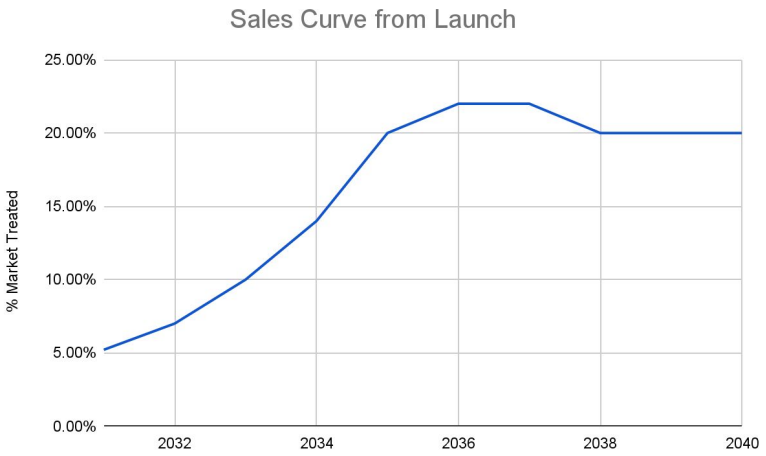


Figure 7: Total and forecasted UK market size per cancer

Assuming the following sales curve, where 2031 represents the completion of Phase III clinical trials captures 5.21% of the SAM, we project peak sales (22% of SAM) in 2036 which equates to 4,116 patients dosed:



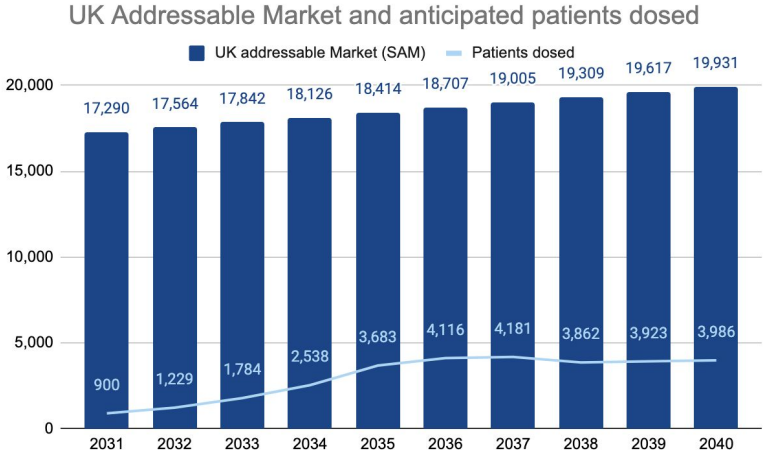


Figure 8: Sales curve from launch, SAM and anticipated patient doses

To meet dose demand, the following commercial scale up process is proposed, using a CDMO for manufacturing.

Approval

Therapy approval reached from MHRA and Ethical approval from Gene Therapy Advisory Committee during Phase III Clinical Trials

Scaling Manufacturing

Manufacturing will be done through Contract Development and Manufacturing Organizations (CDMOs), such as:

CATAPULT Cell and Gene Therapy

The manufacturing process is expected to be relatively simple since the therapy is allogenic and can be produced in batch manufacturing

Exit

The optimal exit strategy would be a buyout by a pharmaceutical before, during or after Phase III clinical trials, in order to pursue international commercialisation, diversification of its application to other solid tumors and beyond.

Sales price is expected to be $3.7M*

*see **Appendix 5** for M&A deal analysis

Financial Plan

Costs

The following outlines a breakdown of R&D and manufacturing costs throughout development until product launch in 2032. Assumptions for costs have been made from historic examples of cell and gene therapy start ups and studies investigating costs associated with allogeneic development (Harrison et al., 2019).

Timeline	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
	Discovery	Preclinical IND filed		Phase I 18 participar	Phase II 200 Participants		Phase III 2700 participants			Launch

R&D costs	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
£ GBP										
New Drug registration MHRA	-	-	-	-	-	-	-	-	5,006	-
IP expenses (patent filing and legal fees)	5,000	-	-	-	-	-	-	-	-	-
Clinical Trial application fee (MHRA)	0	0	0	3,060	0	0	0	0	0	0
Salaries (Sales, General & Admin)	75,000	75,000	100,000	100,000	125,000	150,000	200,000	250,000	300,000	450,000
Clinical and manufacturing costs*	5,000	10,000	10,000	86,640	480,240	480,240	4,320,240	4,320,240	4,320,240	4,320,240
*equvilent to total manufacturing costs detailed below										
Total Costs	85,000	85,000	110,000	189,700	605,240	630,240	4,520,240	4,570,240	4,625,246	4,770,240

Assumptions
MHRA Application made 90 days before the end of trial (GOV.uk) (Harrison et al., 2019)
SG&A salaries increase as therapy approaches launch (Autolus Therapeutics plc, 2022)

Manufacturing costs	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	
£ GBP											
Facility and equiptment	803	803	803	803	803	803	803	803	803	803	18%
Materials (Media, growth factors, QC tests)	1,115	1,115	1,115	1,115	1,115	1,115	1,115	1,115	1,115	1,115	25%
Consumables (Pipettes, cultures, flasks etc)	45	45	45	45	45	45	45	45	45	45	1%
Labour (Operators, Supervisor, Quality control)	2,230	2,230	2,230	2,230	2,230	2,230	2,230	2,230	2,230	2,230	50%
Other (insurance, maintenance, utilities)	268	268	268	268	268	268	268	268	268	268	6%
COGS	4,460	4,460	4,460	4,460	4,460	4,460	4,460	4,460	4,460	4,460	
Fill and finish	200	200	200	200	200	200	200	200	200	200	
Shipping and logistics	140	140	140	140	140	140	140	140	140	140	15%
Cost per dose	**4,800**	**4,800**	**4,800**	**4,800**	**4,800**	**4,800**	**4,800**	**4,800**	**4,800**	**4,800**	
Doses	0	0	0	18	100	100	900	900	900	900	
Failure rate				5%	5%	5%	5%	5%	5%	5%	
Total Manufacturing Costs	**0**	**0**	**0**	**86,640**	**480,240**	**480,240**	**4,320,240**	**4,320,240**	**4,320,240**	**4,320,240**	

Assumptions
Average COGS for Allogenic therapies: $4,460 (Harrison et al., 2019)
(BioProcess International, 2018)
(ten Ham et al., 2020)

Figure 9: R&D and manufacturing costs

Revenues and Profits

The subsequent revenues and net profit of the business can be seen in **Figure 10**, taking into account assumptions for drug pricing x number of units sold (i.e., patients dosed) and variable and fixed costs after launch till 2040. Drug pricing accounts for a curative therapy vs long term treatment and the costs associated with allogeneic adoptive cell therapy development, (Harrison et al., 2019). We assume £10,000 per dose, which reflects the median allogeneic drug price from analyst estimates (Lipsitz et al., 2017).

	Ph III completion	*Launch*			*Peak sales year*					
Product Launch	**2031**	**2032**	**2033**	**2034**	**2035**	**2036**	**2037**	**2038**	**2039**	**2040**
£ GBP										
Total addressable market Global (TAM)	478,097	488,445	499,034	509,869	520,958	532,305	543,916	555,799	567,960	580,405
UK addressable Market (SAM)	17,290	17,564	17,842	18,126	18,414	18,707	19,005	19,309	19,617	19,931
% Market Treated (Sales curve)	5%	7%	10%	14%	20%	22%	22%	20%	20%	20%
Patients dosed	900	1,229	1,784	2,538	3,683	4,116	4,181	3,862	3,923	3,986
Price per dose	-	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000
Lisencing and royalties	-	-	-	-	-	-	-	-	-	-
Revenue	**-**	**12,294,484**	**17,842,146**	**25,375,732**	**36,827,531**	**41,155,311**	**41,811,424**	**38,617,111**	**39,234,276**	**39,862,068**
Cost per dose	-	4,800	4,800	4,800	4,800	4,800	4,800	4,800	4,800	4,800
COGS	-	5,901,352	8,564,230	12,180,351	17,677,215	19,754,549	20,069,484	18,536,213	18,832,453	19,133,793
Gross pofit	-	6,393,132	9,277,916	13,195,381	19,150,316	21,400,762	21,741,941	20,080,898	20,401,824	20,728,275
Operating expenses	-	767,176	1,113,350	1,583,446	2,298,038	2,568,091	2,609,033	2,409,708	2,448,219	2,487,393
Salaries (Sales, General & Admin)	-	450,000	500,000	260,000	350,000	500,000	500,000	500,000	500,000	500,000
Net Profit	**-**	**5,175,956**	**7,664,566**	**11,351,935**	**16,502,278**	**18,332,670**	**18,632,908**	**17,171,190**	**17,453,605**	**17,740,882**

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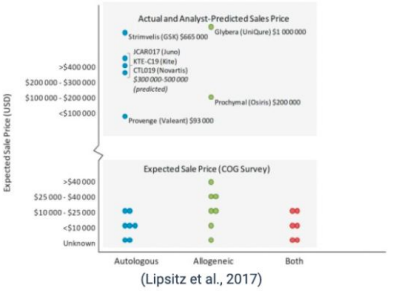
(Adlittle.com, 2013)



(Lipsitz et al., 2017)

Figure 10: Revenues projected from product launch

Return on Investment

Investment required: total costs to reach Phase II completion equate to £1,705,180. Upon larger scale proof of concept at phase III opportunities to partner with larger global pharmaceutical corporations could arise, enabling license agreements to market in the US. Based on licensing deals for adoptive cell immunotherapies that occurred in 2022 (**Appendix 4**) we assume a conservative licensing revenue stream of $6M to occur at Phase III trial stages 2029-2031. Finally, M&A deals within cell and gene therapy between 2021-2022 have been summarized (**Appendix 5)** with an average deal value of $3.7M - highlighting the potential for exit opportunities either during clinical development or post launch. Estimated returns have been shown for a product launch or M&A scenario for the launch year in 2032 (**Appendix 8**), applying a 16% discount rate which is standard for early stage biotech reflects the estimated present value of Ambrosia to be between £1.3 - £1.7 Million. The platform technology offers even greater potential to target combinations of uPAR with other markers identified in appendix 1, such as EGFR, and utilise the emerging cancer hallmark of senescence to treat the unmet need in solid tumors.

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Appendix

Appendix 1: uPAR gene expression in chosen human cancer vs other common targets (Pan-Cancer Atlas, 2023)

mRNA Expression (Amplification) Illumina HiSeq_RNASeqV2

	UPAR (PLAU)	IGF1R	PIK3CA	TP53	KRAS	EGFR
Adrenocortical Carcinoma	72.65642727	1570.912769	405.1502143	1313.7516	848.5956909	383.0696833
Bladder Cancer	5250.081039	1615.42449	445.274133	2056.786762	1657.359385	2649.806316
Breast Cancer	2135.775244	15068.43314	786.1051918	2449.848852	1772.796915	1289.490129
Cervical Cancer	5504.323053	2934.446375	605.5805575	2659.258571	1943.817259	3902.528019
Cholangiocarcinoma	1009.137333	1724.175286	395.91985	2744.413333	1132.546727	920.544
Colorectal Cancer	1162.646509	1712.758635	324.0813809	3672.159877	1708.694948	724.1736519
Endometrial Cancer	1034.405256	3028.660434	513.3554421	4986.579397	1939.855246	612.4570044
Esophagogastric Cancer	2669.891765	3566.13745	769.9517341	2310.392822	5326.664745	3480.683462
Glioblastoma		1758.190545	455.629875	2067.331111	1119.171235	13400.58553
Glioma	310.819975	4625.183158	585.8435263	1654.155174	1441.835727	12889.97657
Head and Neck Cancer	9734.453721	4402.20897	783.3657084	1592.348085	1800.510115	7911.90514
Hepatobiliary Cancer	795.3488667	308.6356824	313.0838266	1658.522615	1005.156225	1415.768908
Leukemia	389.4271517		877.504341	3676.549784		-0.01583
Mature B-Cell Neoplasms	1419.01	228.1714	511.1215333	5089.85	1565.129714	47.73764286
Melanoma	672.504	5338.973314	528.1774946	2365.654114	1080.183487	134.7918751
Miscellaneous Neuroepithelial Tumor						672.94785
Non-Seminomatous Germ Cell Tumor	858.96725	2059.523059	325.6902944	2245.641667	2940.366279	309.5930563
Non-Small Cell Lung Cancer	5834.454368	3708.032654	879.7282201	1979.104325	2317.494779	3675.769655
Ocular Melanoma		7477.455		2956.74875	349.389	44.0394
Ovarian Epithelial Tumor	1766.457575	2951.251882	560.6440091	4109.396504	2784.275457	369.4915436
Pancreatic Cancer	4710.229231	1992.674	568.4147778	1430.95725	1547.844048	851.0349275
Pheochromocytoma	162.243	3823.519071			860.5282727	110.03282
Pleural Mesothelioma	2525.966667	3123.629176	466.8993941	2227.016667	1165.863105	1465.474017
Prostate Cancer	256.2924067	5008.010923	393.3210776		1370.308533	883.7927977
Renal Clear Cell Carcinoma	2594.945417	3182.94344	538.679354	1261.628885	1095.228563	3910.217308
Renal Non-Clear Cell Carcinoma	5181.284	2347.454	347.911751	1450.928648	1232.494485	997.4207398
Sarcoma	6961.910714	2573.89681	499.2580488	1393.796128	1245.012196	1003.726954
Seminoma	638.29175	3065.029394	390.2364167	2251.155	3652.009433	106.9258679
Thymic Epithelial Tumor	1152.6418	2588.014667	607.8084	2820.56	999.65925	1036.2364
Thyroid Cancer	348.069		394.291	1327.269375	890.9802857	666.6955556

Appendix 2: Patient population stratification

Stratification of patient populations	2018	2019	2020	2021	2022	% of patients with UPAR and IGF1R	References
Bladder cancer Stage IV (Global)	16,578	17,149	17,524	17,968	18,451		(Global Data Epidemiology, 2022)
% of stage IV bladder cancer UPAR	13,180	13,633	13,932	14,285	14,669	79.50%	(Ecke et al., 2005)
% of stage IV bladder cancer IGFR1	9,151	9,466	9,673	9,918	10,185	55.20%	(Neuzillet et al., 2017)
UPAR & IGF1R (Global)	7,275	7,526	7,690	7,885	8,097	43.88%	Combined probability of UPAR and IGF1R
Bladder cancer Stage IV (UK)	413	429	436	444	452		
UPAR & IGF1R UK	**181**	**188**	**191**	**195**	**198**		
Breast Cancer Stage IV (Global)	27,488	27,933	28,325	28,695	29,068		(Global Data Epidemiology, 2022)
% of stage IV UPAR	26,663	27,095	27,475	27,834	28,196	97.00%	(Dublin et al., 2000)
% of stage IV IGFR1	13,332	13,548	13,738	13,917	14,098	50.00%	(Farabaugh, Boone and Lee, 2015)
UPAR & IGF1R (Global)	13,332	13,548	13,738	13,917	14,098	48.50%	Combined probability of UPAR and IGF1R
Breast Cancer Stage IV (UK)	2704	2,726	2,751	2,774	2,800		
UPAR & IGF1R UK			**1,334**	**1,345**	**1,358**		
Cervical Cancer Stage IV (Global)	-	-	24,998	25,528	26,061		(Global Data Epidemiology, 2022)
% of stage IV UPAR			16,499	16,848	17,200	66.00%	(Jing et al., 2012)
% of stage IV IGFR1			5,610	5,728	5,848	34.00%	(Moreno-Acosta et al., 2012)
UPAR & IGF1R (Global)			5,610	5,728	5,848	22.44%	Combined probability of UPAR and IGF1R
Cervical Cancer Stage IV (UK)			223	224	225		
UPAR & IGF1R UK			**50**	**50**	**50**		
Head and Neck Cancer Stage IV (Global)	-	-	222,658	227,344	232,632		(Global Data Epidemiology, 2022)
% of stage IV UPAR			220,209	224,843	230,073	98.90%	(Christensen et al., 2022)
% of stage IV IGFR1			127,721	130,409	133,442	58.00%	(Dale et al., 2015)
UPAR & IGF1R (Global)			127,721	130,409	133,442	57.36%	Combined probability of UPAR and IGF1R
Head and Neck Cancer Stage IV (UK)			4,609	4,693	4,741		
UPAR & IGF1R UK			**2,644**	**2,692**	**2,720**		
Esophageal Cancer Stage IV (Global)	97,810	98,408	98,909	99,376	99,834		(Global Data Epidemiology, 2022)
% of stage IV UPAR	87,051	87,583	88,029	88,445	88,852	89.00%	(Liu et al., 2018)
% of stage IV IGFR1	45,266	45,543	45,775	45,991	46,203	52.00%	(Kalinina et al., 2010)
UPAR & IGF1R (Global)	45,266	45,543	45,775	45,991	46,203	46.28%	Combined probability of UPAR and IGF1R
Esophageal Cancer Stage IV (UK)	2,723	2,735	2,746	2,757	2,770		
UPAR & IGF1R UK	**1,260**	**1,266**	**1,271**	**1,276**	**1,282**		
Non-Small Cell Lung Cancer (Global)		422,433	431,381	442,908	454,915		(Global Data Epidemiology, 2022)
% of stage IV UPAR		295,703	301,967	310,036	318,441	70.00%	(Gutova et al., 2007)
% of stage IV IGFR1		173,873	177,556	182,301	187,243	58.80%	(Nurwidya et al., 2016)
UPAR & IGF1R (Global)		**173,873**	**177,556**	**182,301**	**187,243**	41.16%	Combined probability of UPAR and IGF1R
Non-Small Cell Lung Cancer Stage IV (UK)		21,648	22,102	22,462	22,873		
UPAR & IGF1R UK		**8,910**	**9,097**	**9,245**	**9,415**		

Appendix 3: Cancer incidence forecasts

Stratification of patient populations							Forecast											
Global cancer incidence by mutation	**2018**	**2019**	**2020**	**2021**	**2022**	**AGR%**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**	**2031**	**2032**	**2033**	**2034**	**2035**
Bladder cancer Stage IV (Global)	16,578	17,149	17,524	17,968	18,451	*2.71%*	18,951	19,465	19,993	20,536	21,093	21,665	22,252	22,856	23,476	24,112	24,766	25,438	26,128
% of stage IV bladder cancer UPAR	13,180	13,633	13,932	14,285	14,669		15,066	15,475	15,895	16,326	16,769	17,223	17,691	18,170	18,663	19,169	19,689	20,223	20,772
% of stage IV bladder cancer IGFR1	9,151	9,466	9,673	9,918	10,185		10,461	10,745	11,036	11,336	11,643	11,959	12,283	12,616	12,959	13,310	13,671	14,042	14,423
UPAR & IGF1R (Global)	7,275	7,526	7,690	7,885	8,097		8,317	8,542	8,774	9,012	9,256	9,507	9,765	10,030	10,302	10,581	10,868	11,163	11,466
Bladder cancer Stage IV (UK)	413	429	436	444	452	*2.28%*	462	473	484	495	506	518	529	541	554	566	579	593	606
UPAR & IGF1R UK	**181**	**188**	**191**	**195**	**198**		**203**	**208**	**212**	**217**	**222**	**227**	**232**	**238**	**243**	**249**	**254**	**260**	**266**
Breast Cancer Stage IV (Global)	27,488	27,933	28,325	28,695	29,068	*1.41%*	29,477	29,892	30,312	30,739	31,171	31,610	32,055	32,506	32,963	33,427	33,897	34,374	34,858
% of stage IV UPAR	26,663	27,095	27,475	27,834	28,196		28,593	28,995	29,403	29,817	30,236	30,662	31,093	31,531	31,974	32,424	32,880	33,343	33,812
% of stage IV IGFR1	13,744	13,967	14,163	14,348	14,534		14,738	14,946	15,156	15,369	15,586	15,805	16,027	16,253	16,482	16,713	16,949	17,187	17,429
UPAR & IGF1R (Global)	13,332	13,548	13,738	13,917	14,098		14,296	14,497	14,701	14,908	15,118	15,331	15,547	15,765	15,987	16,212	16,440	16,671	16,906
Breast Cancer Stage IV (UK)	2704	2,726	2,751	2,774	2,800	*0.88%*	2,825	2,849	2,874	2,899	2,925	2,950	2,976	3,002	3,029	3,055	3,082	3,109	3,136
UPAR & IGF1R UK	**1,311**	**1,322**	**1,334**	**1,345**	**1,358**		**1,370**	**1,382**	**1,394**	**1,406**	**1,419**	**1,431**	**1,443**	**1,456**	**1,469**	**1,482**	**1,495**	**1,508**	**1,521**
Cervical Cancer Stage IV (Global)	-	-	24,998	25,528	26,061	*2.10%*	26,609	27,169	27,741	28,325	28,920	29,529	30,150	30,785	31,432	32,094	32,769	33,458	34,162
% of stage IV UPAR			16,499	16,848	17,200		17,562	17,932	18,309	18,694	19,088	19,489	19,899	20,318	20,745	21,182	21,628	22,083	22,547
% of stage IV IGFR1			8,499	8,680	8,861		9,047	9,238	9,432	9,630	9,833	10,040	10,251	10,467	10,687	10,912	11,141	11,376	11,615
UPAR & IGF1R (Global)			5,610	5,728	5,848		5,971	6,097	6,225	6,356	6,490	6,626	6,766	6,908	7,053	7,202	7,353	7,508	7,666
Cervical Cancer Stage IV (UK)			223	224	225	*0.45%*	226	227	228	229	230	231	232	233	234	235	236	237	238
UPAR & IGF1R UK			**50**	**50**	**50**		**51**	**51**	**51**	**51**	**52**	**52**	**52**	**52**	**53**	**53**	**53**	**53**	**54**
Head and Neck Cancer Stage IV (Global)	-	-	222,658	227,344	232,632	*2.22%*	237,785	243,053	248,437	253,940	259,566	265,316	271,193	277,201	283,341	289,618	296,033	302,591	309,294
% of stage IV UPAR			220,209	224,843	230,073		235,170	240,379	245,704	251,147	256,710	262,397	268,210	274,151	280,224	286,432	292,777	299,263	305,892
% of stage IV IGFR1			129,142	131,860	134,927		137,915	140,971	144,093	147,285	150,548	153,883	157,292	160,776	164,338	167,978	171,699	175,503	179,391
UPAR & IGF1R (Global)			127,721	130,409	133,442		136,398	139,420	142,508	145,665	148,892	152,190	155,562	159,008	162,530	166,131	169,811	173,572	177,417
Head and Neck Cancer Stage IV (UK)			4,609	4,693	4,741	*1.42%*	4,808	4,877	4,946	5,016	5,088	5,160	5,233	5,308	5,383	5,460	5,538	5,616	5,696
UPAR & IGF1R UK			**2,644**	**2,692**	**2,720**		**2,758**	**2,797**	**2,837**	**2,878**	**2,918**	**2,960**	**3,002**	**3,045**	**3,088**	**3,132**	**3,176**	**3,222**	**3,267**
Esophageal Cancer Stage IV (Global)	97,810	98,408	98,909	99,376	99,834	*0.51%*	100,347	100,862	101,379	101,900	102,423	102,949	103,477	104,009	104,542	105,079	105,619	106,161	106,706
% of stage IV UPAR	87,051	87,583	88,029	88,445	88,852		89,308	89,767	90,228	90,691	91,156	91,624	92,095	92,568	93,043	93,520	94,001	94,483	94,968
% of stage IV IGFR1	50,861	51,172	51,433	51,676	51,914		52,180	52,448	52,717	52,988	53,260	53,533	53,808	54,084	54,362	54,641	54,922	55,204	55,487
UPAR & IGF1R (Global)	45,266	45,543	45,775	45,991	46,203		46,440	46,679	46,918	47,159	47,401	47,645	47,889	48,135	48,382	48,631	48,880	49,131	49,383
Esophageal Cancer Stage IV (UK)	2,723	2,735	2,746	2,757	2,770	*0.43%*	2,782	2,794	2,806	2,818	2,830	2,842	2,854	2,866	2,879	2,891	2,903	2,916	2,928
UPAR & IGF1R UK	**1,260**	**1,266**	**1,271**	**1,276**	**1,282**		**1,287**	**1,293**	**1,299**	**1,304**	**1,310**	**1,315**	**1,321**	**1,327**	**1,332**	**1,338**	**1,344**	**1,349**	**1,355**
Non-Small Cell Lung Cancer (Global)	-	422,433	431,381	442,908	454,915	*2.50%*	466,288	477,946	489,895	502,142	514,696	527,564	540,753	554,273	568,130	582,333	596,892	611,815	627,111
% of stage IV UPAR		295,703	301,967	310,036	318,441		326,402	334,562	342,926	351,500	360,287	369,295	378,527	387,991	397,691	407,633	417,824	428,270	438,977
% of stage IV IGFR1		248,391	253,652	260,430	267,490		274,177	281,032	288,058	295,260	302,641	310,208	317,963	325,912	334,060	342,412	350,973	359,747	368,741
UPAR & IGF1R (Global)		173,873	177,556	182,301	187,243		191,924	196,722	201,641	206,682	211,849	217,145	222,574	228,139	233,842	239,688	245,681	251,823	258,119
Non-Small Cell Lung Cancer Stage IV (UK)		21,648	22,102	22,462	22,873	*1.85%*	23,297	23,728	24,167	24,615	25,071	25,535	26,008	26,489	26,980	27,479	27,988	28,507	29,034
UPAR & IGF1R UK		**8,910**	**9,097**	**9,245**	**9,415**		**9,589**	**9,766**	**9,947**	**10,131**	**10,319**	**10,510**	**10,705**	**10,903**	**11,105**	**11,311**	**11,520**	**11,733**	**11,951**
TAM (Global Market)			378,090	386,232	394,932		403,347	411,958	420,768	429,783	439,007	448,445	458,103	467,985	478,097	488,445	499,034	509,869	520,958
SAM (UK Market)			14,587	14,804	15,023		15,258	15,497	15,740	15,988	16,239	16,495	16,756	17,020	17,290	17,564	17,842	18,126	18,414

Appendix 4: Licensing Agreements for adoptive cell therapies in 2022

Licensing Agreements in Adoptive Cell Therapies

Source: Global Data, Advanced Deals Data; Deal type: Mergers & Acquisitions,Strategic Alliances, Deal From Date, Drug Descriptor: Adoptive Cell Therapy

Announcement	Total Deal Value ($/€ M)	Geography	Year	Upfront payment
Sanofi Enters into Licensing Agreement with Scribe Therapeutics	$1,025	France , United States	2022	$25 million
Roche to Enter into Licensing Agreement with Poseida Therapeutics	$6,135	United States	2022	$110 million upfront
Xyphos Biosciences Enters into Licensing Agreement with GO Therapeutics	$784	United States	2022	$20 million upfront
Bristol Myers Squibb Enters into Licensing Agreement with Century Therapeutics	$3,000	United States	2022	$100 million
Cabaletta Bio Enters into Licensing Agreement with IASO Biotherapeutics	$162	United States, China	2022	$162 million
Xenetic Biosciences Enters into Licensing Agreement with CLS Therapeutics	$14	United States	2022	$500,000
CellPoint Enters into Licensing Agreement with Shenzhen Pregene Biopharma	€22	Global	2022	€20 million (contingent on milstones)
BioNTech Enters into Licensing Agreement with Medigene	€29	United States	2022	€26 million
ONK Therapeutics Enters into Licensing Agreement with Intellia Therapeutics	$920	United States	2022	$184 million (per product development)
Sana Biotech Enters into Licensing Agreement with IASO Biotherapeutics and Innovent Biologics	$204	China , United States	2022	Unknown

Appendix 5: Average deal value in CGT biotech 2021-2022

Average Deal Value in Cell and Gene therapy 2021-2022: $3.7M

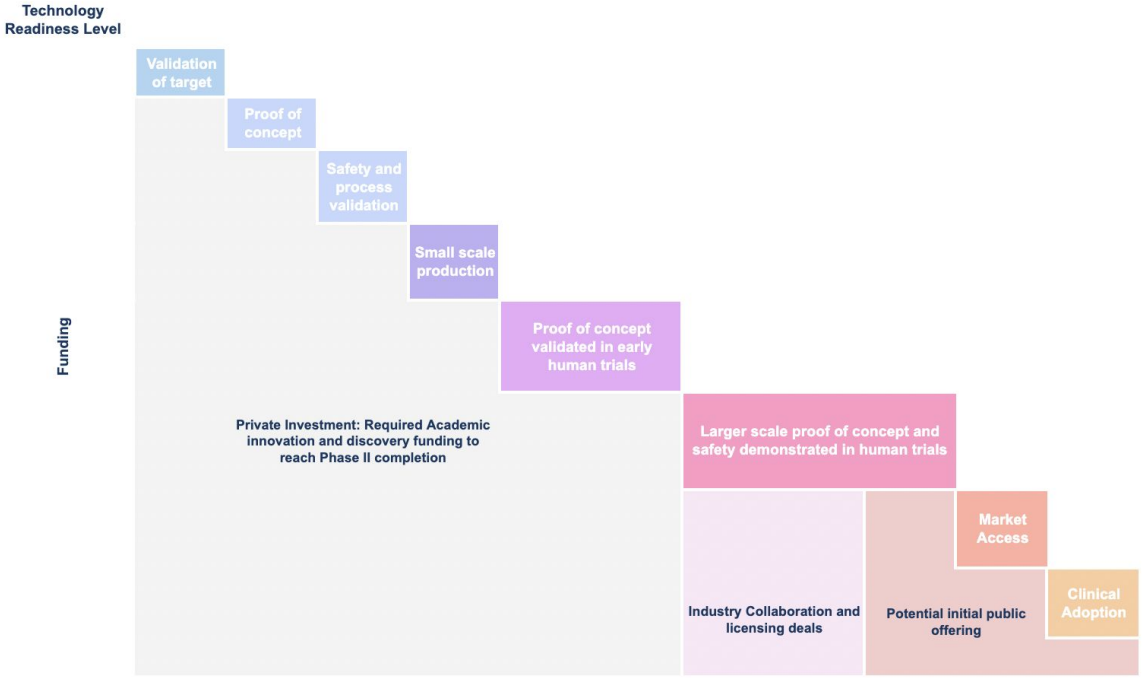
Acquirer	Target	Deal Size $M	Year
Pfizer	Global Blood therapeutics	5,146	2022
Amgen	ChemoCentryx	3,658	2022
BMS	Turning Point Therapeutics	3,053	2022
GSK	Affinivax	3,300	2022
Pfizer	Biohaven Pharma	11,912	2022
Genentech	Adaptimmune	3,650	2021
Kite	Shoreline Biosciences	2,300	2021
Merck	Artiva Biotherapeutics	1,881	2021
Takeda	Immusoft Corp	900	2021
Takeda	KSQ Therapeutics	900	2021

References

Biotech M&A since Pfizer;s Biohaven deal Khandekar, A. and Leo, L. (2022)

Next-Gen Partnerships: The Ascent of Advanced Therapies, Ward, M. (2022)

Appendix 6: Technology readiness level



Appendix 7: Studies identifying uPAR across cancers

Prostate cancer	(Wach et al., 2019) (Li and Cozzi, 2007) (Ertongur et al., 2004)
Breast Cancer	(Costantini et al., 1996) (Huber et al., 2016)
Colon Cancer	(Jessup, 1994)
Bladder Cancer	(Hau et al., 2017) (Skovgaard et al., 2016)
Ovarian cancer	(Sier et al., 1998) (Minopoli et al., 2019)
Head and neck cancer	(Boonstra et al., 2017)
Cervical cancer	(Jing et al., 2012)
Pancreatic cancer	(Loosen et al., 2019)
Lung cancer	(Pedersen et al., 1994)
Renal cell carcinoma	(Wagner et al., 1995)
Liver cancer	(Morita et al., 1997) (Dubuisson et al., 2000)
Gastric cancer	(Yonemura et al., 1997) (Park et al., 2011)

Appendix 8: Investment required and return on investment

Investment required to reach Ph II completion: 1,705,180

Product launch and licensncing scenario	2032	
Projected net revenue (UK only)	5,175,956	
Licensing revenue	1,000,000	
Total (Terminal Value)	6,175,956	
ROI ratio	2.62	ROI ratio: (Net income - initial investment) / initial investment
Terminal Value	6,175,956	
Discount rate	16%	
Discount period	9	2023 to 2032
Discount Factor	26.30%	Discount Factor: 1 / (1 + Discount Rate) ^ Period
PV of Terminal Value	1,623,986	Terminal value x discount factor

M&A buy out scenario	2032	
Projected net revenue (UK only)	5,175,956	
M&A Deal Value	3,670	
Total (Terminal Value)	5,179,626	
ROI ratio	2.04	ROI ratio: (Net income - initial investment) / initial investment
Terminal Value	5,179,626	
Discount rate	16%	
Discount period	9	2023 to 2032
Discount Factor	26.30%	Discount Factor: 1 / (1 + Discount Rate) ^ Period
PV of Terminal Value	1,361,998	Terminal value x discount factor