Bioengineering Game Changing Technology: a horizon scan of genetically engineered technologies

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Conflicts of interest

The authors declare no conflict of interest.

NIHR | Innovation Observatory

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Abstract

Background

Bioengineering bridges biology and engineering to develop technologies that address health-related problems, and it has therefore become one of the most impactful and fast-growing fields in healthcare. As this field continues to evolve rapidly, staying informed about promising technologies is essential for effectively applying new advancements to medical research and healthcare. In 2024-25, the NIHR Innovation Observatory (IO) undertook horizon scans to identify bioengineering applications in healthcare, with this report focussing on therapeutics and drug delivery. Early, horizon scanning enables the exploration of opportunities, leading to the timely adoption of new technologies.

Aim

This report aims to identify new areas and technologies within genetic engineering, as well as to highlight emerging technologies or under-researched areas. The goal is to identify emerging bioengineered genetic technologies with the potential to be game-changing; that is, to offer new solutions to health problems or re-purpose an existing technology for a new application.

Methods

This study used a novel, exploratory search method to generate a large number of results relevant to bioengineering. These terms were then first screened, cleaned, then grouped into clusters and visualised using VOSviewer, and finally those identified in VOSviewer as being particularly high frequency or new were then further analysed by searching for applications in bibliographic databases and clinicaltrials.gov.

Results

Most Frequent Keywords and Applications

Six keywords were identified using the novel methodology. The three most frequent were “CRISPR”, “microRNA” and “Saccharomyces cerevisiae”. Applications of these included using gene editing to alter the invasiveness of bladder cancer microtumours, using gene therapies to locally delivery microRNA (miRNA) to treat epilepsy, and S. cerevisiae being used to create therapeutics for immune support in Parkinson’s disease.

Newest Keywords and Applications

The three keywords defined as newest were “Staphylococcus epidermidis”, “arginine” and “Herpesviridae”. Applications of these included an engineered S. epidermidis strain for the treatment of Netherton syndrome, engineering CAR-T cells to make their own arginine to attack cancer cells, and genetically altered herpes simplex virus to treat bladder cancer.

Discussion

The new methodology was targeted, repeatable and objective, and identified a large and comprehensive dataset. This rigorous and objective approach ensures that keywords found are those most likely related to game-changing technologies. The limitations included the horizon scan nature of the work: it aimed to identify new technology, rather than assess these in depth. The method searched only one bibliographic database and clinical trials registry, but it was comprehensive and avoided errors associated with format conversion and data cleaning. The method helped to address a key issue in emerging genetic bioengineered products, identifying them at an early stage in order to plan for changes in pathways and policy that may present.

Importantly, the findings contribute to genetic engineering research by highlighting areas where innovation is actively addressing unmet needs such as the limited precision of conventional therapies and off-target affects. Genetic engineering research is advancing quickly with CRISPR and miRNA technologies following on from well-established recombinant vaccines. Most technologies were found to be at a mid-level technology readiness (5-7) with most preclinical literature showing that many of these technologies may still require significant research to become commercially viable. The complexity of the technologies and licensing pathways could suggest more support is needed in funding and policy to ensure patients gain timely access to advances.

Conclusion
This horizon scan used a new method to identify technologies with the potential to provide new solutions to unmet needs within genetic engineering. Some technologies could have important roles in addressing important national issues, such as antimicrobial resistance, and help to give patients access to more personalised medical care. This study demonstrates the utility of a novel horizon-scanning method to identify transformative genetic engineering technologies. These findings could inform policy, funding, and research priorities, ultimately improving patient access to innovative healthcare solutions.

Background

Bioengineering bridges biology and engineering to develop technologies that address health-related problems. Advances in both engineering and biology have allowed bioengineering to drive progress in many medical technologies, such as phage therapies[1] (pg 19), cell based therapies[1] (pg 23), and gene therapies (pg 19).[1] As bioengineering continues to revolutionise medical technology, it has become one of the most impactful and fast-growing fields in healthcare. Estimates of the 2024 value of the global genetic engineering market range from US$1.49 billion[2] to $1.7 billion.[3] The market for genetic engineering is also predicted to reach around $2.9 billion by 2033, at a compound annual growth rate of 6.74%.[2] As this field continues to evolve rapidly, staying informed about promising technologies is essential for effectively applying new advancements to medical research and healthcare.

Therefore, in 2024-25, the NIHR Innovation Observatory undertook horizon scans to identify bioengineering applications in healthcare, focussing on tissues and medical devices, therapeutics and drug delivery systems and genetically engineered organisms. Horizon scanning plays an important role in facilitating the integration of new technologies into healthcare. By identifying emerging technologies early, horizon scanning enables the exploration of opportunities, leading to the timely adoption of new technologies. As well as guiding research priorities, early identification of innovations enables health organisations to prepare for their implementation and minimises delays in patient access to innovative treatments.

Horizon scanning is particularly valuable in the rapidly advancing field of bioengineering, since its interdisciplinary and complex nature presents significant challenges in transitioning from

research to clinical practice. Regulatory hurdles present a considerable challenge, as novel bioengineering approaches often fall outside traditional frameworks. As noted by Taylor (2014), these technologies span multiple domains, such as pharmaceuticals, medical devices, biologics and surgical procedures, which are each governed by distinct regulatory frameworks and, at times, different oversight bodies.[4] The complexity of genetically engineered technologies and potential for unintended and possibly permanent consequences for the recipient, poses challenges for risk assessments and regulatory decision making that is not always present in other forms of innovations. Additionally, genetic engineering has additional ethical challenges: for example, between 1999-2006, researchers tested a gene therapy treatment to restore function of gamma c in immune cells in children. Unfortunately, five of the children later developed leukaemia as the newly transferred gene had encoded into the wrong gene, highlighting vital safety concerns for future developments.[5] Public perception is also a major hurdle as attitudes to these technologies vary widely.[6]

Another major obstacle is the "Valley of Death," the critical funding gap between early-stage research and successful clinical adoption.[7] Many genetic disorders that would benefit from genetic engineering treatments are considered extremely rare, with some affecting only 1 in every million: this presents as a barrier to companies developing these technologies as they may not be able to reclaim the high costs of development. Other more common diseases, such as cancer, can benefit from genetically engineering a patient's own cells to create a personalised treatment. Whilst this is effective, the personalised nature means that the technology cannot be mass produced, meaning that companies may not be able to recover the costs outside of the rare disease space.[5]

Genetic engineering is a key part of bioengineering as it comprises genome editing, a "group of technologies with the ability to directly modify an organism's DNA through a targeted intervention in the genome".[8] One of the most important and widely used applications is clustered regularly interspaced short palindromic repeats (CRISPR). It is used as both gene therapy (as a drug to repair a defective or mutated gene) or cell therapy (to make the body's cells attack toxic cells or regenerate beneficial cells).[9] This latter type of application underpinned Casgevy, a drug made by editing stem cells using CRISPR to produce more foetal haemoglobin. It was approved in 2024 and is used in blood disorders such as beta thalassaemia and sickle cell disease. The approval of Casgevy for blood disorders provides a strong example of the real-world application of genetic engineering.[10]

Aim

This report aims to identify novel genetic technologies and under-researched areas in bioengineering, as well as to highlight emerging technologies or under-researched areas. Under-researched areas are defined in this context as those that appear less frequently in bibliographic searches, and which are relatively new to the field. By focusing on topics with limited current literature in areas with significant market potential and unmet clinical need, the report seeks to highlight opportunities for increased research and funding

The goal is to identify emerging genetic bioengineered technologies with the potential to be game-changing; that is, to offer new solutions to health problems or re-purpose an existing technology for a new application. Here, we use the NIHR Innovation Observatory definition[1] of emerging technology as being the "horizon of the unknowns, [where] we identify potentially disruptive technologies that may have significant impact… This horizon is populated with patent intelligence and early research such as conference abstracts. Funders keen to progress early innovation are also a good source of signals. In some fields published and grey literature dealing with exploratory preclinical or very early clinical literature can be used to triangulate against these sources."

Scope

We followed the "HIP-D" framework (Horizon, Innovation, Population and Data source), as shown in Table 1. Interested parties could include funders, accelerators and catapults, Government departments, policy makers, regulators, health technology assessors, SMEs, patient groups and charities.

Framework item	Scope
Horizon	Emerging (from 15 years to market to present); all technology readiness levels; all clinical trial phases (including preclinical research)
Innovation	New technology; new application of existing technology
Population	Unspecified
Data source	Published literature (using Embase/Ovid). No study type limits; date limits January 2020-January 2025. Further searches also carried out in clinicaltrials.gov.

Table 1 application of the "HIP-D" framework

Embase was selected as it is a large biomedical database and includes MEDLINE (the principle component of PubMed)[2] with extensive search limited options and an advanced search function.[3] The decision to begin the time threshold as 2020 was based on an article by The American Society of Mechanical Engineers.[11] This society is one of the leading global organisations developing codes and standards. It focuses on technical, educational and research issues of the engineering and technology community and one of its divisions focuses on bioengineering.[12]

[1] https://io.nihr.ac.uk/what-we-do/emerging-horizon/
[2] https://guides.library.uab.edu/lhldatabases/embase
[3] https://kemh.libguides.com/research/FAQ_Database_differences

Methods

As bioengineering is a broad topic which covers an extensive research landscape, this method was developed to transform complex bibliometric data into maps and keywords that provide direction for more efficient and targeted searches. The method is used in all three arms of the bioengineering project and is described in detail in a separate report. This section is an overview of the general method used as well as where methods specific to this arm were used.

The project used a novel, exploratory search method to generate a large number of results relevant to bioengineering. These results were then first screened, then grouped into clusters and visualised using VOSviewer, and finally those identified as being particularly high frequency or new were further analysed by searching for applications in bibliographic databases and clinicaltrials.gov. Finally, a preliminary analysis was carried out of the link between these keywords and unmet needs. The overall process is shown in **Error! Reference source not found.**. Limitations are examined in the discussion section.

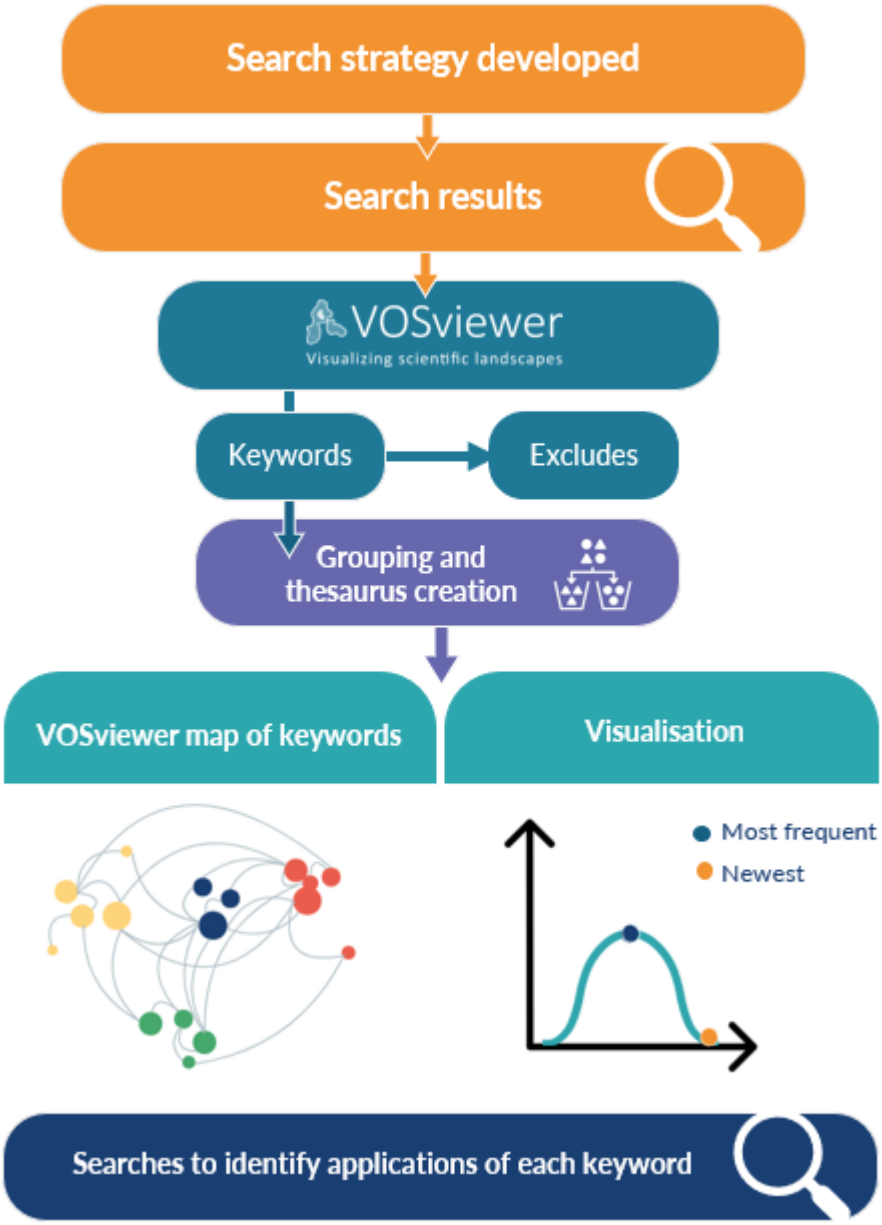

Figure 1 Overview of the method used. Image credit: Katie Twentyman.

VOSviewer

VOSviewer[4] is a free open-source bibliometric visualisation tool which creates maps of keywords based on co-occurrence data, enabling the examination of clusters of intelligence. These clusters represent interconnected themes or concepts within the dataset, providing insights into patterns of innovation.[13] Words and phrases that are strongly associated with only

[4] www.vosviewer.com

one or only a few topics in the body of literature are identified using semantic analysis, and are included in the term map. These terms are not only domain-specific but that also have a high discriminatory power, which is important to visualise the structure of the field.[14] The terms are located relative to each other, such that the distance between two is an approximate measure of their similarity within the set, where similarity is defined as the extent to which they refer to or link to each other. Highly related terms are then indicated as clusters.[15]

The advantages of VOSviewer are that it supports a broad range of sources including PubMed, Lena and OpenAlex; it is user-friendly; and visualisations can be shared.[16] Although it has a small number of limitations, such as its inability to produce other visualisations such as tree maps, these are not relevant to the current study.

Search strategy

A bibliographic search was developed in January 2025 by an information specialist in Embase (OVID). Free-text English search strings were used, including terms for 'bioengineering', 'genetically engineered', and 'synthetic biology' developed through recent literature (see Appendix 1).[17-20] EndNote 21 was used as the repository for the bibliometric sources found. The search was subsequently peer reviewed by another information specialist.

To maximise intelligence to be discovered from the text, the unspecified search field (.mp) was used. The unspecified search field covers multiple fields simultaneously including title, abstract, heading word, and keyword heading word. This ensures that the search is thorough and captures relevant information from various parts of the record and increases the likelihood of retrieving relevant results that would otherwise be missed if searched individually. Subject headings are predefined controlled vocabulary that is often used to standardise content which in information retrieval is used to maximise the possibility of retrieving records. However, the decision was made following scoping searches to use free-text terms which offer specificity over standardised controlled vocabulary.

The decision of time threshold from 2020 was based on an article by The American Society of Mechanical Engineers[11]. This society is one of the leading organizations in the world developing codes and standards and focuses on technical, educational and research issues of the engineering and technology community; one of its divisions focuses on bioengineering.[12]

Keywords

Results from the bibliographic search were downloaded as a RIS file before being uploaded to VOSviewer (v 1.6.20). Criteria settings: type of analysis, co-occurrence; counting method, full counting; threshold, minimum number of documents of a keyword 5; number of keywords to be selected, 4266 (maximum). VOSviewer generated a keyword list of 4266 items which was downloaded into Excel.

Eligibility criteria

Technologies were included in the "genetics" category if they met the following inclusion criteria:

1. The biology being engineered is within the patient or organism
2. There was evidence of its use in the past four years
3. There was evidence that it was being used for a specific application

The exclusion criteria were:

1. A diagnostic, assay or imaging device such as spectroscopy, since these were unlikely to include bioengineering
2. A well-established technology unless there was evidence that it had a new application
3. Very general terminology or redundant such as "walking"
4. An irrelevant keyword such as "side effect"
5. Any keyword not directly related to humans, such as "sheep" or "plant cell"

Thesaurus and creation of keywords list

A thesaurus was created to refine keywords for genetic engineering. The thesaurus enhances the quality of the dataset as it removes duplicates, corrects errors and inconsistences, and consolidates different versions of the same term (for example, due to UK/US English spelling variations) to ensure uniform treatment, improving accuracy for analysis. This is especially valuable when dealing with large datasets to improve the readability of the maps and therefore make them easier to interpret. To produce thesaurus lists specific to bioengineering and genetics, the keyword list underwent a selection and refinement process and the 119 keywords relating to genetic engineering were assigned to this category. A further 2201 keywords were excluded or grouped under a single term due to spelling convention or synonyms. This grouping was simply to place terms under a single umbrella term: the information could still be accessed. An example here is grouping the keywords "liver", "liver cell", "liver organoid" and "liver tissue" under the umbrella term "liver". Finally, keywords relating to unmet needs were also identified. These included diseases such as "cancer", areas of application with in the body such as "inflammation" or an organ or tissue such as "kidney".

Creation of VOSviewer maps

Once the selection and refinement process were completed, the thesaurus files were input into VOSviewer along with the bibliographic search RIS file to produce a keyword map for analysis. Criteria settings: type of analysis, co-occurrence; counting method, full counting; threshold, minimum number of documents of a keyword 5; number of keywords to be selected, maximum. Where necessary the keywords were deduplicated before input.

Data analysis

The VOSviewer map file was exported as a .csv file and converted to an .xlsx file for analysis in Microsoft Excel. VOSviewer grouped the keywords into 10 clusters, although analysis took place across all keywords. The overall most frequently occurring and newest keywords were analysed, with the rationale that the most common keywords are those most frequently mentioned in the literature, representing a strong signal and thus high research interest (indicated with blue dot in Figure 1). However, high-frequency keywords were not assumed to indicate positive research outcomes: for example, papers are sometimes published when a new technology fails or has a negative effect. Therefore, the keywords were used as the basis for further searches in various databases, as described below, and the sources read carefully to ensure that the technology could lead to a benefit and had the potential to be game-changing.

Since focusing on the most frequently cited keywords could introduce bias towards well-established and higher-cited technologies, we also investigated those appearing at a low frequency. The low frequency keywords appear at both ends of the curve, representing the oldest and newest technologies found. Therefore, to ensure that we only analysed newer technologies, with the potential to be game-changing, we restricted the analysis of low-occurrence keywords to this latter category, indicated by the orange dot in Figure 2. The limitations of this method are discussed below.

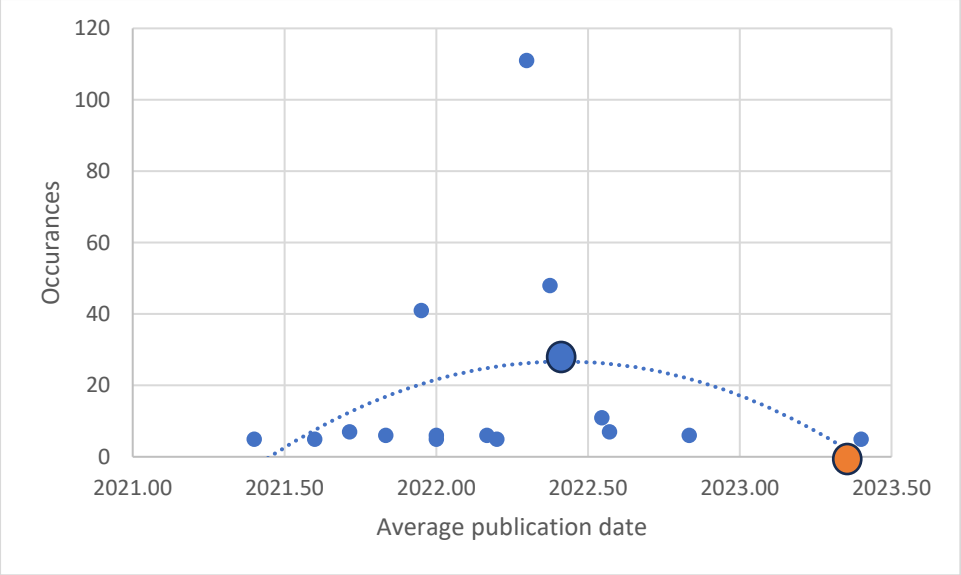

Figure 2: distribution of occurrences of keywords against mean publication date. Trendline is a 2nd order polynomial function. Example taken from Cluster 1: the largest cluster for genetic engineering.

Mean publication dates were extracted from VOSviewer as the mean value of all publication dates for that keyword. To ensure validity, a sample of six keywords (the three most and three least frequent in Cluster 1) were analysed. Their mean publication years were extracted from

VOSviewer and compared to the mean publication year in EndNote. As can be seen in Table 2, the maximum difference between the two was 1.1 months, and a paired two-tailed T-test revealed no significant difference (P = 0.7787). This indicates that the publication date given by VOSviewer was valid.

	Mean publication year		
Keyword	VOSviewer	EndNote	Difference (months)
CRISPR	2021.89	2022.08	0.19
MicroRNA	2022.30	2022.19	0.11
Saccharomyces cerevisiae	2021.67	2022.02	0.35
Staphylococcus epidermidis	2023.20	2022.50	0.7
Arginine	2023.40	2022.30	1.1
Herpesviridae	2023.40	N/A	N/A

Table 2. There was no significant difference in mean publication years between VOSviewer and EndNote. Herpesviridae has a value of N/A due to no papers included with this keyword.

Search terms for further analysis of keywords

Applications of the most and least frequently-occurring new keywords were then searched for in the FDA[5], EMA[6] and MHRA[7] medical databases. The searches, which took place in September 2025, consisted of searching for the keyword itself. Most searches returned no results, and the few that did were largely irrelevant. The EMA search for CRISPR found Casgevy; and the EMA search for Herpesviridae returned results for attenuated vaccines and the Shingrix recombinant vaccine (both of which also appear in later searches and are discussed further below).

Therefore, these keywords were searched for in three databases: 1) in May-July 2025 clinicaltrials.gov (including trial phase and primary completion date (PCD) as an indicator of technology readiness level); 2) in April-May 2025 the original Embase search in EndNote; and 3) since the Embase search was carried out in January 2025, PubMed was searched with a date range of 1/1/2025-31/7/2025 to identify work published since the Embase search. Search criteria were as follows unless otherwise stated and some examples relating to genetic engineering were found for each keyword per source. Primary research articles were prioritised over reviews, since the purpose of these is to review existing literature, rather than presenting cutting-edge findings. When included, reviews were carefully selected to ensure they presented findings into the latest developments.

1. clinicaltrials.gov: Other terms: *[keyword]* | Not yet recruiting, Recruiting, Active, not recruiting, Completed, Terminated studies | Phase: Early Phase 1, 1, 2, 3, 4 | Study start on or after 01/01/2020

2. Embase (via EndNote): search for *[keyword]* in the Abstract field. Identified articles were then tagged with the keyword for ease of future retrieval and sorted by date. Searching began with the newest papers and abstracts were read to identify relevant technologies.

3. PubMed: search for *[keyword]* in primary research articles published since 1 January 2025. Results were then sorted by date, with the search starting at the newest article.

Inclusion criteria

Examples were only included where the technology itself formed part or all of the intervention under test, rather than being used as a placebo, vehicle or measurement technique. For example, trial NCT06527534 was excluded as it measured miRNA levels in the patient blood sample, with no genetic modification. Included records related to genetic engineering, with clear application to a medical or healthcare context. Protocols were excluded, as were records that described the development, preparation or improvement of the technology, with no mention of an application. Terminated trials were only included if the termination was due to reaching goal recruitment early.

Assessment of technology readiness level (TRL)

While identifying individual examples of applications for each keyword has merit, of greater utility is to map keywords to their technology readiness level (TRL), since this provides policymakers and funders with an overview of where technologies lie in the pipeline. TRLs are "a type of measurement system used to assess the maturity level of a particular technology"[5], and provide a common understanding of the status of a technology[6]. We used two methods to categorise TRLs: the first provided by UK Research and Innovation[7] as the investors of £8 billion of UK taxpayers' money each year into research and innovation[8] (Figure 3); and the second provided by[9] the Utrecht Health Seed Fund, who invests in science-based startups in life sciences/medtech, digital innovation and sustainability. These latter definitions more

[5]https://www.ukri.org/councils/stfc/guidance-for-applicants/check-if-youre-eligible-for-funding/eligibility-of-technology-readiness-levels-trl/
[6] https://www.defproc.co.uk/insights/technology-readiness-level-trl-explained
[7]https://www.ukri.org/wp-content/uploads/2022/01/EPSRC-11012022-Technologyreadinesslevelsfrombasicresearchtoadoptionanddiffusion.pdf
[8] https://www.ukri.org/
[9] https://uhsf.nl/wp-content/uploads/2020/02/TRL_overview_UHSF_version20200206.pdf

clearly match TRL to clinical trial phase. We only mapped results from clinical trials due to both the volume and variety of results from bibliographic sources. Clinical trials that did reported phase were less common than those that did not, meaning that we took a random sample of 20% of this latter type. Although this improved feasibility, we acknowledge that the sample may not have been fully representative: therefore, these results should be interpreted cautiously. The eligibility criteria were the same as those given in the Inclusion Criteria section above

We used these definitions to map the keywords to TRLs as follows. First, if trial webpage contained the name of the technology, a brief Google search was performed to identify if it was already marketed for the indication on test: if it was, this was categorised as TRL9. If the technology was already marketed and a different application was being tested, the TRL was categorised based on the current trial. When stated, trial phase and status (for example completed phase III trial) were used to categorise each record. Trials which did not state the phase were categorised based on if the trial was of the safety or efficacy of the technology and its status. If the same technology was identified in more than one trial, it was only counted once, and the highest TRL taken.

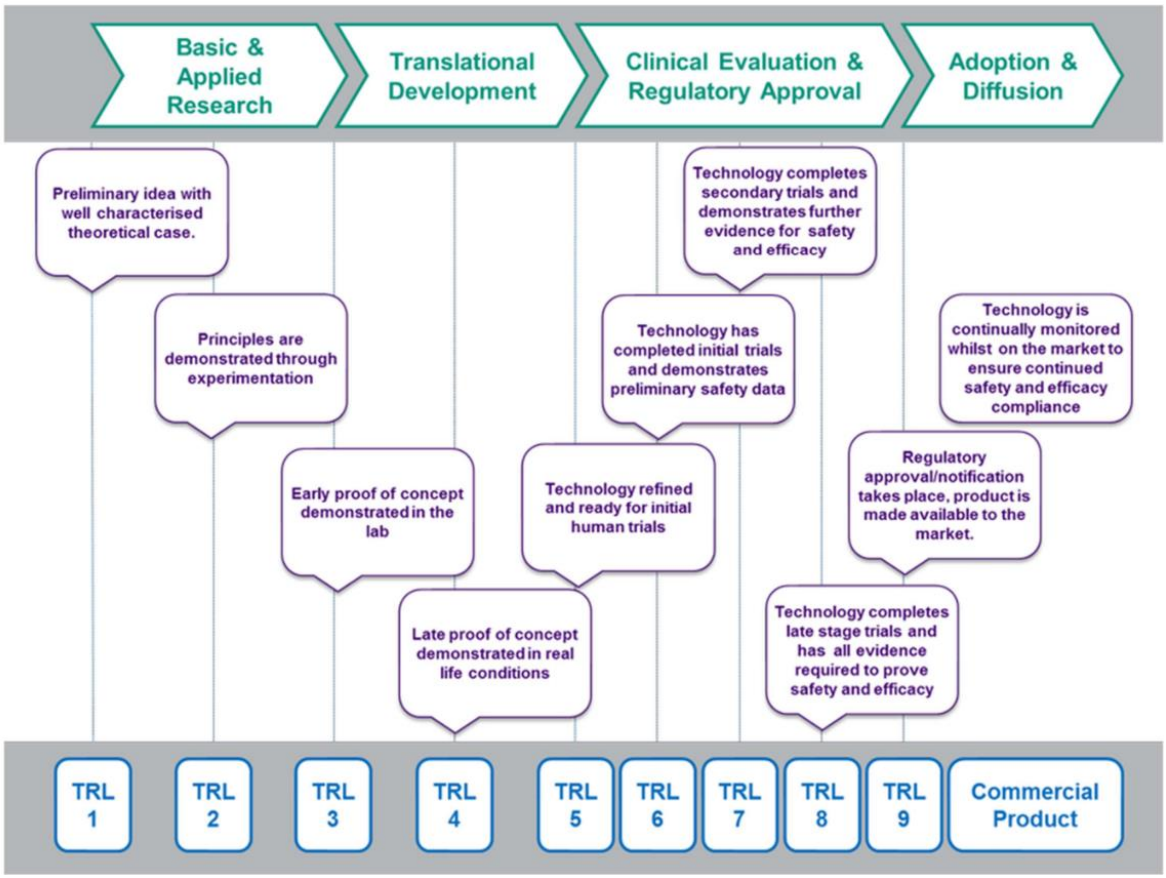

Figure 3. Flowchart taken from UKRI website[10] showing how technologies were categorised in TRL stages with TRL1 being the lowest level of development, and TRL9 being a licensed product. Links to trial phases can also be seen e.g. TRL5 being early or ongoing phase 1 trials.

Link between keywords and unmet needs

One goal of this project was to determine if the method could be used to detect potential applications of the identified technologies. Therefore, each keyword was combined with a thesaurus for the unmet needs and used to create a map in VOSviewer (Figure 4).

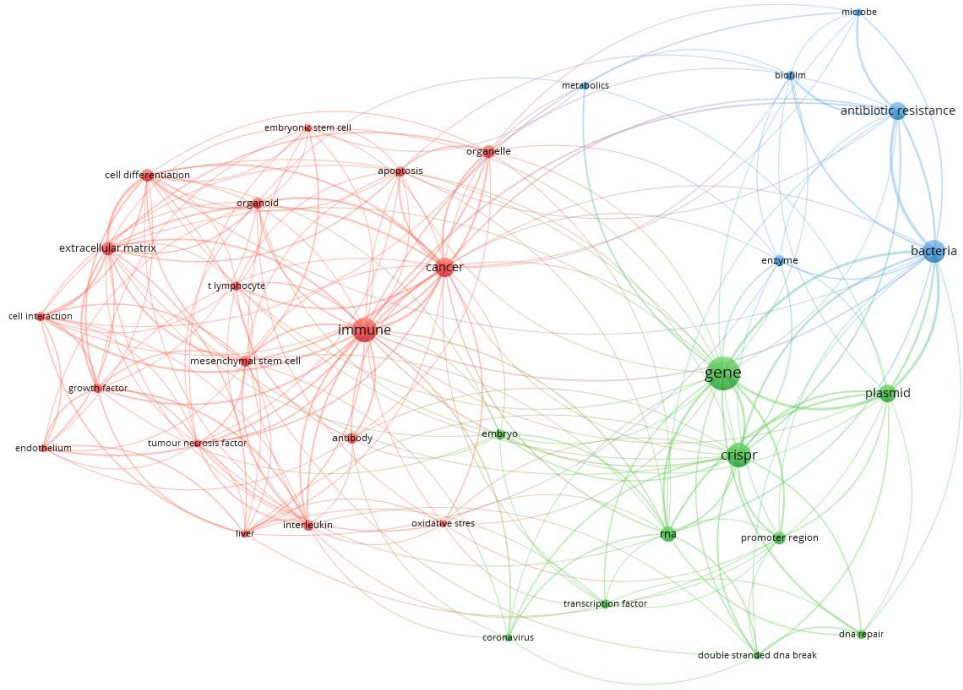

Figure 4 A VOSviewer map showing the links between a selected keyword (CRISPR) and the identified unmet needs.

A thesaurus specific to unmet needs was created as described in the "Thesaurus and creation of keywords list" section. A library for each keyword was created by searching for it in the "keyword" field in Endnote, then exporting the library as a .txt file. A VOSviewer map was created (Figure 5), then the map and network files were exported as .csv files and converted to .xlsx files for analysis in Microsoft Excel. The network file gives a numerical value for the link strength between two nodes. The top three unmet needs were identified for each keyword for

[10]https://www.ukri.org/wp-content/uploads/2022/01/EPSRC-11012022-Technologyreadinesslevelsfrombasicresearchtoadoptionanddiffusion.pdf

further analysis: this involved searching for the unmet need in the database of clinical trials for research currently being undertaken to fulfil these needs/applications.

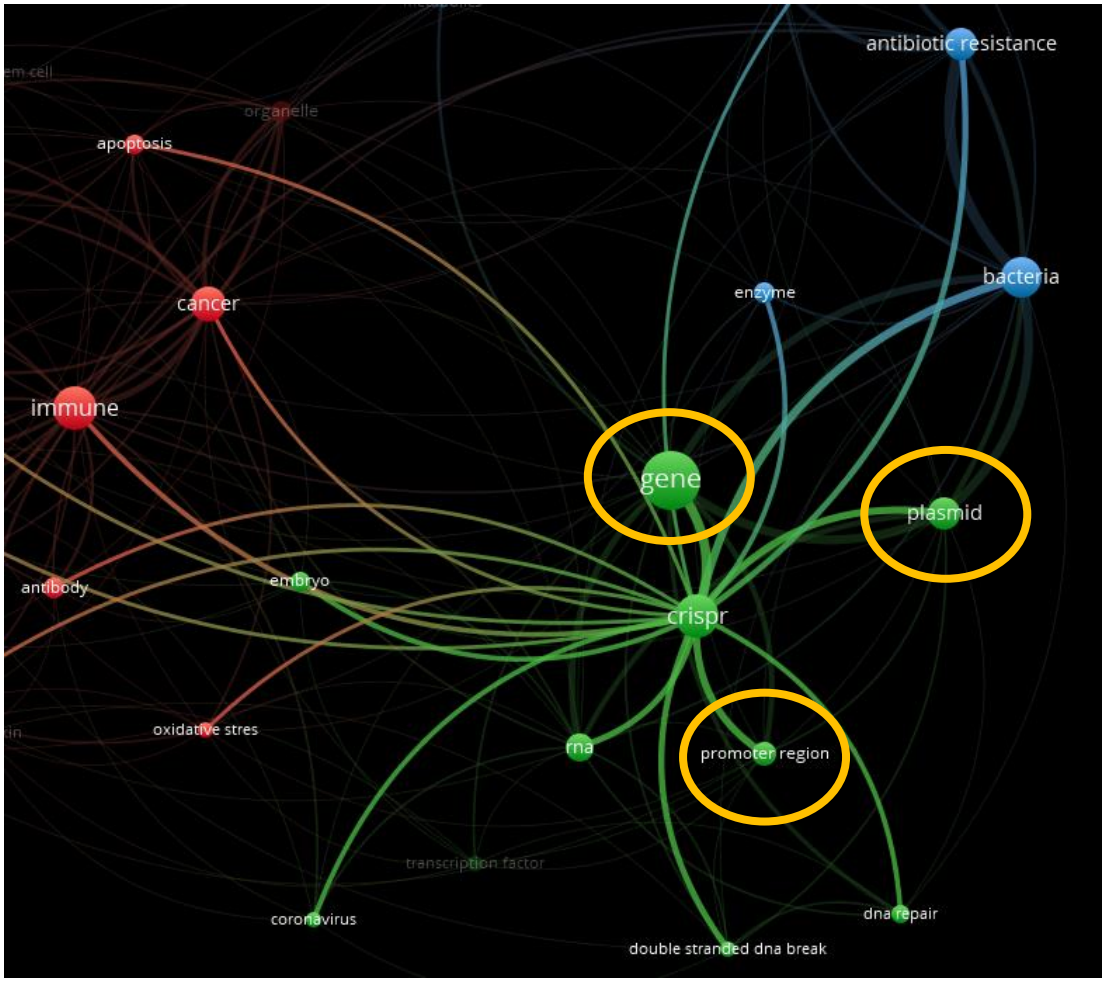

Figure 5 a close-up of the links between a selected keyword (CRISPR) and the top three applications (gene, plasmid and promoter region). The dark background was selected to emphasise the width of the top three links

As discussed in the methodology limitations section in the Discussion, this method demonstrated proof of concept. However, further searches were required to ensure results were specific to the current project, and time constraints prevented these. Therefore, findings from this section should currently be interpreted as preliminary evidence reflecting the proof of concept demonstrated by this method.

Expert engagement

The overall game-changing tech project comprises three arms: tissues and medical devices; therapeutics and drug delivery; and genetic engineering (the current project). These three arms were agreed at project outset with the Department of Health and Social Care.

Quality assurance

Various steps were taken to maximise the quality of the project. First, the search strategy was peer reviewed by a second, experienced information specialist. Secondly, a pilot screen was undertaken by all three reviewers (PA, RP and MF), who were blinded to the others' decisions. This was followed by peer review, which helped to guide the groupings for the technologies found. The inter-rater agreement was 93.76%. While using a simple percentage has drawbacks, the figure is well above the 80% previously stated as the minimum acceptable interrater agreement.[21] Finally, the methods and preliminary results were discussed and peer-reviewed by a senior member of the IO leadership team.

Results

Figure 6 shows the overall visualisation of keywords, and the links between them, produced in VOSviewer. There are a total of 10 clusters, each represented in a different colour. Each cluster is made up of the circles ("nodes") that represent a keyword and the links between them (known as "edges"). The size of each node indicates its occurrence; and the size of each edge the strength of the link between two nodes. This maps the links between themes and key which allowed us to analyse the terms in groups are well as individually.

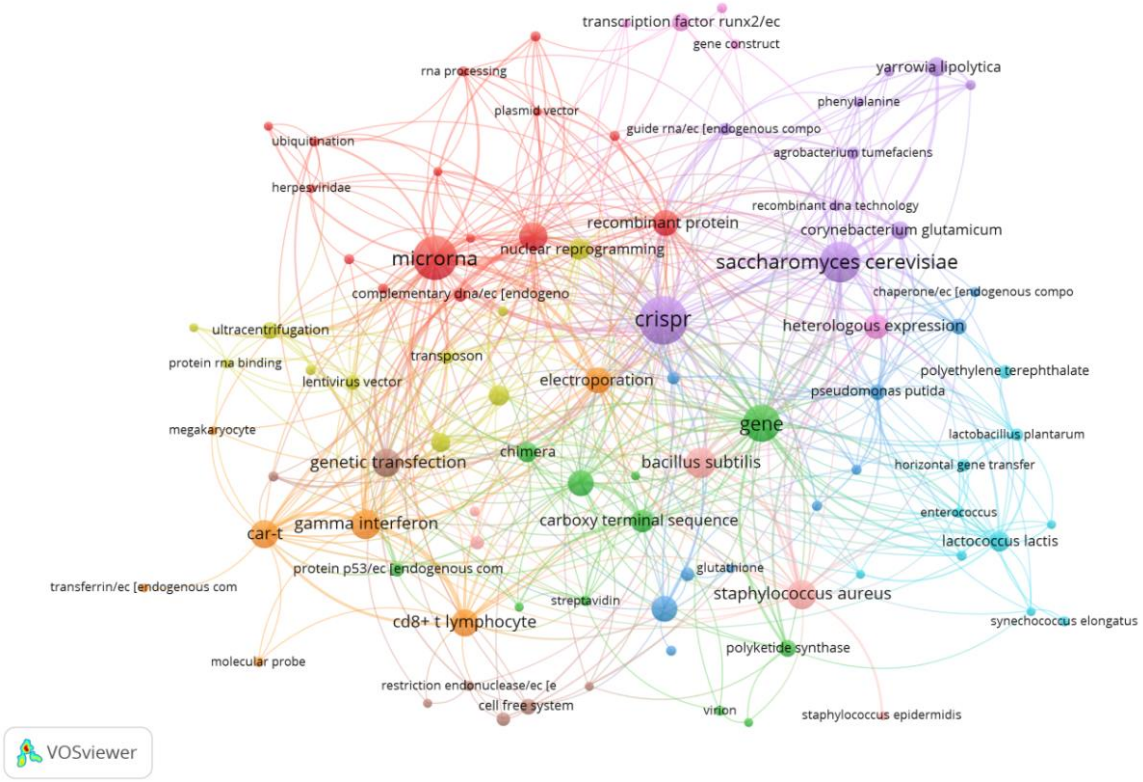

Figure 6 Overall genetic engineering keyword visualisation in VOSviewer

A total of 90 keywords were extracted from 10 clusters (see Tables S1-12 in Appendix A). We focused on the three most frequently occurring keywords, as well as the three least frequently occurring words that had the most recent data published e.g. newest. This focus was used to identify the newest technologies that may be deemed game-changing in the field, but as of yet have little data attached.

Keyword (VOSviewer occurrences)	Mean publication date	CT.gov (final total from which examples taken)	Embase	PubMed
Crispr (135)	2021.89	61(1)	83	1105
MicroRNA (111)	2022.30	215(8)	32	1510
Saccharomyces cerevisiae (98)	2021.67	28(1)	52	143
Staphylococcus epidermidis (5)	2023.40	13(0)	2	20
Arginine (5)	2023.40	241(11)	15	233
Herpesviridae (5)	2023.40	260(22)	0	198

Table 3 showing the three most frequent (shaded in blue) and three newest keywords (shaded in orange). The asterisk represents where the numbers are from a more focused search.

Analysis of most frequent keywords

Note that the sub-headings for clinicaltrials.gov and PubMed are clickable hyperlinks directly to the search results page. The full hyperlink is given as a footnote for offline versions of this report.

CRISPR

Clinicaltrials.gov[11]

A total of 61 studies were found and only one had published results. 50 of the identified trials reported the phase of development. Seven trials were terminated. 49 trials were included as per the criteria, but two trials were found to be investigating the same technology in the same disease, so the duplicates were removed. 21 technologies were found to have TRL5 (45%), 22 technologies had TRL6 (47%), and four technologies had TRL7 (8%). No technologies were found to be above TRL7 as none of the trials were reported to have completed phase 3 or be licensed for the indication (Figure 8). The mean TRL was 5.63. One example of a technology found was CRISPR-Cas9 genome editing on donor liver grafts to reduce immunogenicity before transplantation (NCT07053488; TRL 5)- this could address one of the main causes of transplant failure in patients and reduce the need for life-long immunosuppression treatments.

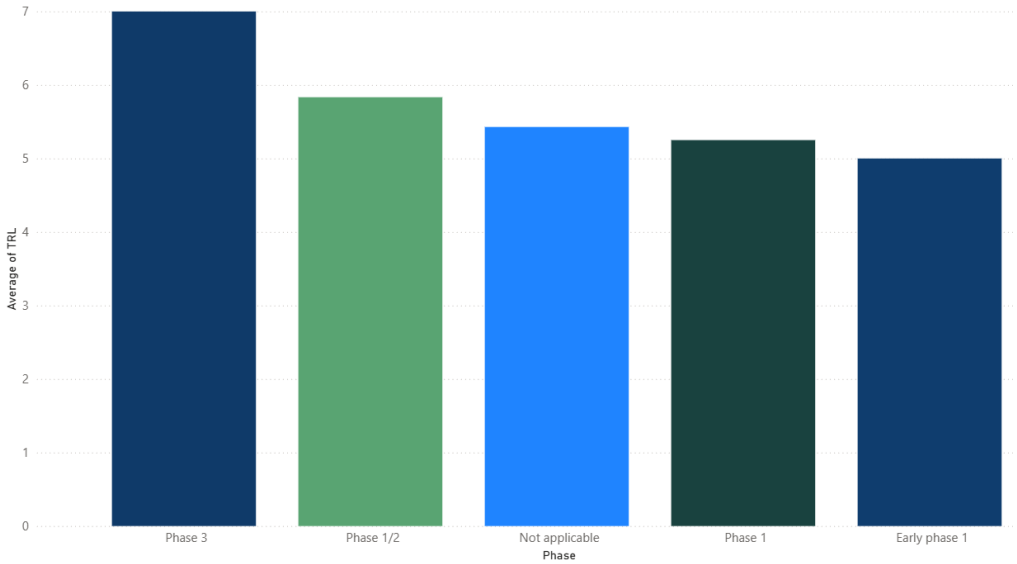

Figure 8 showing the average TRL for technologies in each phase of development in trials.

[11] https://www.clinicaltrials.gov/search?term=crispr&start=2020-01-01_&aggFilters=phase:0%201%202%203%204,status:not%20rec%20act%20com%20ter

three most frequent (shaded in blue) and three newest keywords (shaded in orange). The asterisk represents where the numbers are from a more focused search.

EMBASE

Of the 83 records identified, three relevant examples were:

1. Phage therapy and use in establishing standard antimicrobials to combat multidrug resistant bacterial pathogens.[22]
2. CRISPR-Cas13 is also in development to kill antibiotic resistant bacteria: it is used to reprogram eukaryotes to combat pathogenic RNA viruses and in the regulation of gene expression, facilitating the knockdown of mRNA, circular RNA, and noncoding RNA.[23]
3. CRISPR-Cas9 gene editing is being investigated to knock out NOTHC1 genes to alter the invasiveness of bladder cancer microtumours.[24]

PubMed[12]

1105 studies were identified in our search, but only a small number were relevant to genetic engineering. Some of the relevant examples included:

1. Cell-based gene therapy with CRISPR/Cas9 is being used in the treatment of sickle cell disease by targeting the defective HBB gene. [25]
2. CRISPR-Cas9 gene editing has been examined for use in common cardiovascular diseases such as heart disease.[26]
3. CRISPR-Cas systems being used to knock out antibiotic resistance genes or mobile genetic elements to create 'smart antibiotics'.[27]

Overall, the findings from PubMed show that the research into the use of CRISPR is developing form targeting single genes such as HBB, into more complex areas such as the range of genes involved in cardiovascular diseases as a whole as well as the complexities seen in tackling antibiotic resistance which would tackle a global health issue.

Links to most common applications

Application	Strength of link
Gene	6
Plasmid	4
Promoter region	4
Double stranded DNA break	3
RNA	3
DNA repair	2

12 https://pubmed.ncbi.nlm.nih.gov/?term=%28crispr%29+AND+%28%28%222025%2F01%2F01%22%5BDate+-+Publication%5D+%3A+%223000%22%5BDate+-+Publication%5D%29%29&filter=datesearch.y_1&filter=pubt.review&sort=pubdate&sort_order=asc

Embryo	2
Enzyme	2
Immune	2
Extracellular matrix	1
Liver	1
Microbe	1
Oxidative	1

Table 5 Applications with the strongest links to CRISPR

The three applications with the greatest links strengths to CRISPR were: gene (6), plasmid (4) and promotor region (4) (table 5). All 69 trials identified in the clinical trials search for 'crispr' also appeared when adding 'gene' to the search terms, therefore the maximum TRL found for this unmet need link is 7.

MicroRNA

Clinicaltrials.gov[13]

215 studies were found, of which 11 were terminated and 10 had published results. Of the 215, 142 did not report the trial phase. Of these 215 trials only 11 met the inclusion criteria to be assessed for TRL. Two technologies had TRL5 (18%), seven TRL6 (64%), and two had TRL7 (18%). No technologies had a TRL higher than 7 and the average TRL was 6.00. An example of a technology using miRNA is AMT-260, a gene therapy that locally delivers miRNA in adults with unilateral refractory mesial temporal lobe epilepsy (NCT06063850; TRL6). The majority of trials were in TRL6, indicating advanced development of this technology.

[13] https://www.clinicaltrials.gov/search?term=Microrna&start=2020-01-01_&aggFilters=phase:0%201%202%203%204,status:not%20rec%20act%20com

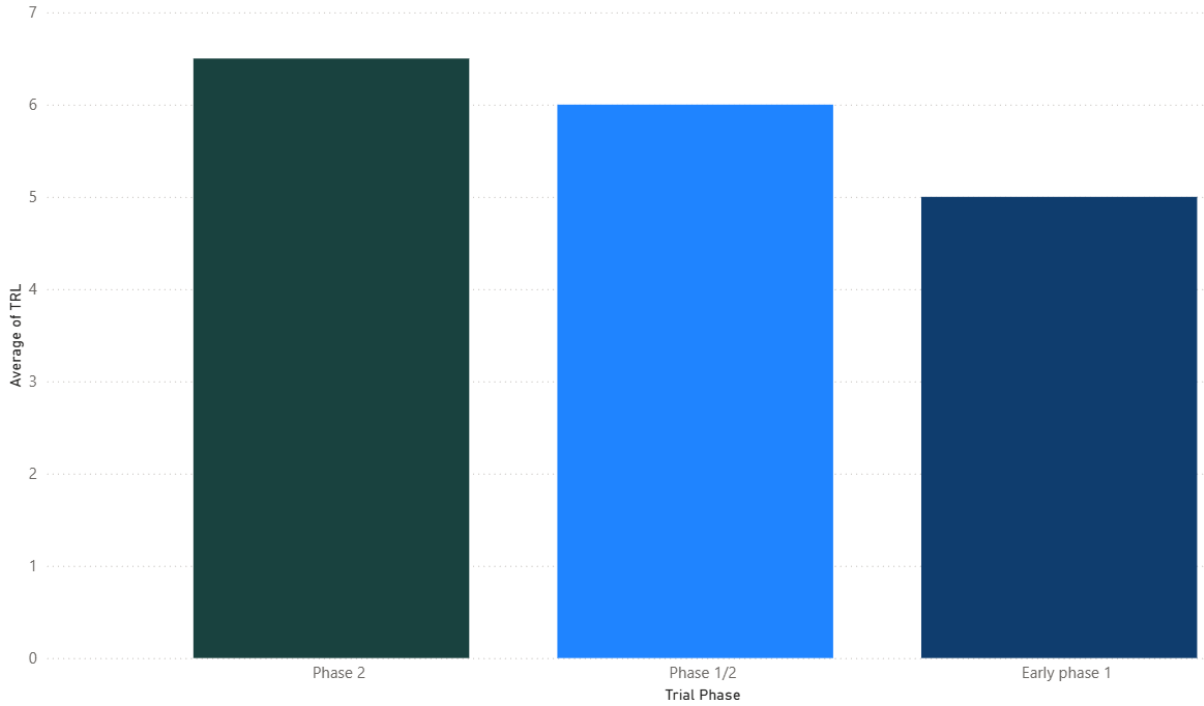

Figure 7 showing the average TRL for technologies in each phase of development in trials.

EMBASE

32 references were found through our search, some relevant examples being:

1. Bone-targeted gene therapy that reverses alveolar bone loss in patients with osteoporosis by targeting the adaptor protein Schnurri-3.[28]
2. miRNA dysregulation has been implicated in rheumatoid arthritis and therefore is being examined as a therapeutic target.[29]
3. miR-467a-3p and miR-874-5p are being investigated to help regulate the stemness and myogenesis of satellite cells, which are dysregulated in sarcopenia.[30]

PubMed[14]

1510 results were identified through PubMed. Relevant examples included:

1. miRNAs have been found to strongly influence hypertension by modulating vascular, renal and other physiological mechanisms. Therefore, research is investigating how

14 https://pubmed.ncbi.nlm.nih.gov/?term=%28microrna%29+AND+%28%28%222025%2F01%2F01%22%5BDate+-+Publication%5D+%3A+%223000%22%5BDate+-+Publication%5D%29%29&filter=dates.2025%2F1%2F1-3000%2F12%2F12&filter=pubt.review&sort=pubdate&sort_order=asc

miRNAs could be inserted into the molecular system that underlies the regulation of blood pressure and subsequent hypertension.[31]

2. miRNA-based therapeutics have been tested and used to treat multiple sclerosis including miRNA restoration therapy (lentivirus expressing a specific type of miRNA and miRNA mimic) and miRNA inhibition therapy such as antisense oligonucleotides, small molecules inhibitors, locked nucleic acids , anti-miRNAs, and antagomirs.[32]
3. miRNA-455-3-P has been identified as a potential biomarker and therapeutic target for Alzheimer's Disease (AD). Several genes implicated in the pathogenesis of AD are directly targeted by miR-455-3p. This regulates important physiological processes associated with the disease, such as the processing of the amyloid precursor protein (APP), TGF-β signalling, the regulation of oxidative stress, mitochondrial biogenesis, and synaptic damages. Models where this gene is removed show improved cognitive function, memory and lifespan compared with wildtype.[33]

Links to most common applications

Application	Strength of link
Organelle	66
RNA	30
Vasculature	16
Oxidative stress	14
Vasculotropin	14
Tumour growth	12
Tumour necrosis factor	12
Transcription factor	11
Organoid	8
Phagocytosis	8
Regulatory t lymphocyte	8
Wound	7
Nervous system inflammation	6
Phosphatidylinositol 3,4,5 trisphosphate 3 phosphatase	6
Protein kinase	6
RNA polymerase	6
Stem cell	6
T lymphocyte	6
Toll like receptor	6
Neural stem cell	5
Osteoarthritis	5
Pancreas cancer	5
Reactive oxygen metabolite	5
Plasmid	4
Pancreas	3

Table 6 Applications with the strongest links to microRNA

The three applications with the greatest links strengths to miRNA were: organelle (66), RNA (30) and vasculature (16). Three trials were identified by combining 'microRNA' and 'organelle' as search terms. One relevant trial was found, using exosome therapy to treat COVID-19 (NCT05216562 [TRL7]).

Saccharomyces cerevisiae

Clinicaltrials.gov[15]

28 trials were identified, but only one had results. Three trials were terminated and 14 did not report trial phase. Of these trials, only four met our inclusion criteria. One technology was found to have a TRL9, one TRL7, and two TRL6 (50%), making the average TRL 7.00 (Figure 9). The high TRL of 7 may be reflective of the organism being well-characterised due to wide use in industry as the bacterium is often used in large scale manufacturing and is known as 'bakers yeast'.[34] One example of Saccharomyces cerevisiae as a genetically engineered treatment is using Sargramostim (a recombinant human GM-CSF produced by recombinant DNA technology using S. cerevisiae) to treat patients with Parkinson's disease (NCT05677633: TRL6).

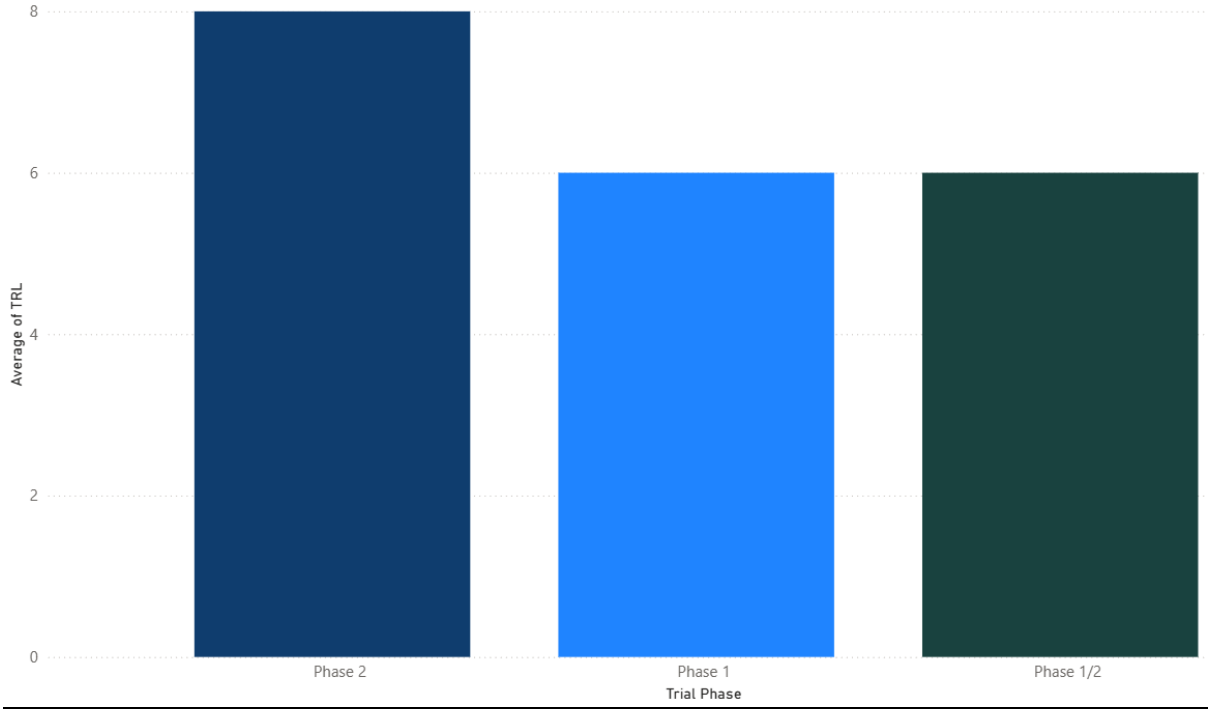

Figure 9 showing the average TRL for technologies in each phase of development in trials.

EMBASE

Of the 52 results identified, many were not within scope as they discussed the use of the yeast in industries outside of health or with no genetic engineering aspect. Relevant examples included:

[15] https://www.clinicaltrials.gov/search?term=saccharomyces%20cerevisiae&start=2020-01-01_&aggFilters=phase:0%201%202%203%204,status:not%20rec%20act%20com

1. Medicarpin, created with bioengineered S. cerevisiae, is an important bioactive compound with multiple medicinal activities, including anti-tumour, anti-osteoporosis, and anti-bacterial effects.[35]
2. Genetically modified S. cerevisiae was used to produce the capsaicinoid nonivamide, which is an active ingredient in pharmaceuticals for the treatment of pain.[36]
3. Genetically engineered S. cerevisiae was used to produce polpunonic acid which is the precursor to the anti-obesity agent celastrol. Celastrol sensitises patients to the hormone leptin which is involved in the feeling of hunger and therefore treatment with this product could help to treat obesity.[37]

PubMed[16]

143 results were identified through the PubMed search but, like the EMBASE results, few were relevant. Some examples that incorporated genetic engineering include:

1. Engineering Saccharomyces cerevisiae for medical applications has been widely studied as it can be used as a 'cell factory' for pharmaceuticals and vaccines, as well as a live biotherapeutic product for the smart *in situ* treatment of intestinal ailments.[38]
2. It has also been studied for use in age-related diseases as it can help to mitigate the inflammation process associated with the multifaceted decline in the elderly.[39]
3. Saccharomyces cerevisiae has also been investigated in the development of epitope-based recombinant protein vaccines against SARS-CoV-2 which utilised the expression system of the yeast cells to neutralise the pathogen.[40]

Links to most common applications

Application	**Strength of link**
Transcription factor	8
Synthetase	5

Table 7 Applications with the strongest links to saccharomyces cerevisiae

The two applications with the greatest links strengths to Saccharomyces cerevisiae were: transcription factor (8) and synthetase (5). No trials were found with links between either 'transcription factor' or 'synthetase' and Saccharomyces cerevisiae.

16 https://pubmed.ncbi.nlm.nih.gov/?term=%28Saccharomyces+cerevisiae%29+AND+%28%28%222025%2F01%2F01%22%5BDate+-+Publication%5D+%3A+%223000%22%5BDate+-+Publication%5D%29%29&filter=dates.2025%2F1%2F1-3000%2F12%2F12&filter=pubt.review&sort=pubdate&sort_order=asc

Analysis of least frequent but newest keywords

Staphylococcus epidermidis

Clinicaltrials.gov[17]

13 trials were identified in the search, none of which had published results, none were terminated, and six of these did not state the trial phase. Only two trials met the inclusion criteria, one had TRL6 and the remaining technology a TRL5 giving an average of TRL5.5- this shows use of this technology is in the earlier stages with lower phase clinical trials showing that it is further from Market Access (Figure 10). One example of a technology is ATR12-351 which is a genetically engineered S. epidermidis strain used to treat the underlying causes of Netherton syndrome (NCT06137157; TRL5).

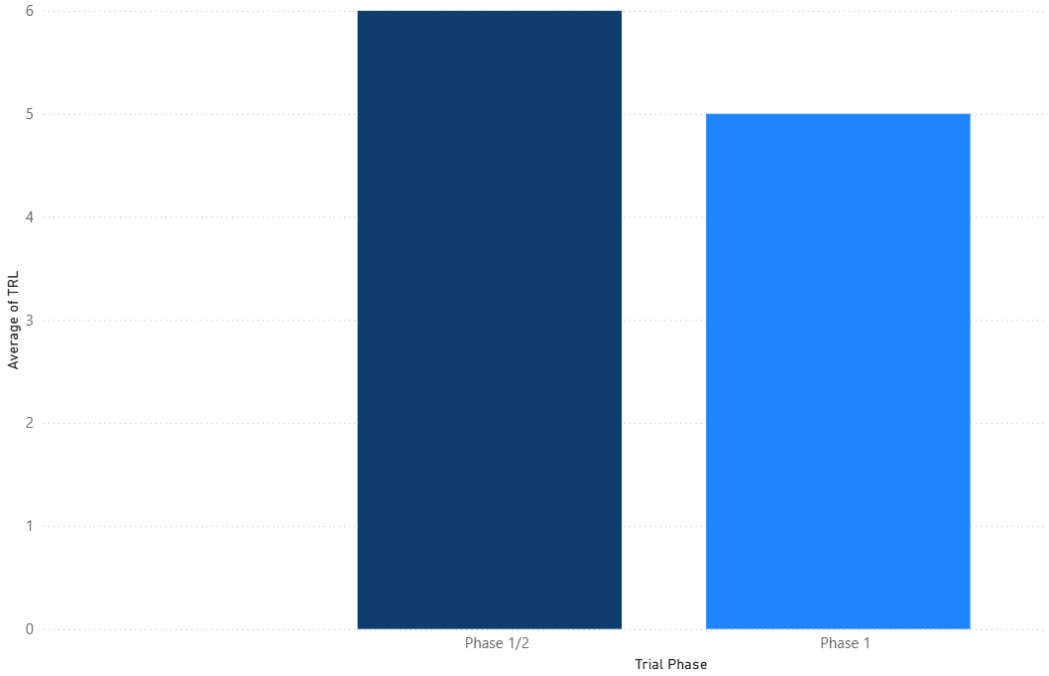

Figure 10 showing the average TRL for technologies in each phase of development in trials.

EMBASE

[17] https://www.clinicaltrials.gov/search?term=staphylococcus%20epidermidis&start=2020-01-01_&aggFilters=phase:0%201%202%203%204,status:not%20rec%20act%20com%20ter

Only two papers were identified through this search, but neither included a genetic engineering component, therefore both were excluded.

PubMed[18]

20 papers were found in the search but only two were relevant to our criteria.

1. S. epidermidis has been genetically engineered to create extracellular vesicles which are used in management of skin inflammation and skin ageing as they can help to mediate host-microbe communication.[41]
2. Coagulase-negative staphylococci (CoNS) are commensal bacteria of the human skin and mucosal membranes. The incidence of nosocomial infections caused by these species is on the rise, leading to a potential increase in antibiotic tolerance and resistance. Phages are emerging as a promising alternative to combat CoNS infections. Scientists are isolating phages infecting CoNS with a particular interest in S. epidermidis.[42]

Links to most common applications

Application	Strength of link
Wound	2

Table 8 Application with a link to staphylococcus epidermidis

Only one application was found to have a link to S. epidermidis and that was wound (2). Six trials were found when searching for both 'staphylococcus epidermidis' and 'wound' but none were found to be relevant in using the bacteria in a genetic engineering capacity.

Arginine

Clinicaltrials.gov[19]

241 trials were found for arginine with seven of these being terminated, 11 reporting results, and 119 not reporting trial phase. Of these 241 trials, only five met our inclusion criteria to be assessed for TRL. The low number of trials meeting the inclusion criteria was reflective of arginine being a semi-essential amino acid that plays a role many bodily functions, therefore it

18 https://pubmed.ncbi.nlm.nih.gov/?term=%28Staphylococcus+epidermidis%29+AND+%28%28%222025%2F01%2F01%22%5BDate+-+Publication%5D+%3A+%223000%22%5BDate+-+Publication%5D%29%29&filter=dates.2025%2F1%2F1-3000%2F12%2F12&filter=pubt.review&sort=pubdate&sort_order=asc

19 https://www.clinicaltrials.gov/search?term=arginine&start=2020-01-01_&aggFilters=phase:0%201%202%203%204,status:not%20rec%20act%20com%20ter

appeared as a keyword in many trails that did not have a genetically engineered focus. Two technologies had a TRL9 (40%), and three TRL5 (60%), giving an average TRL of 6.6 (Figure 11). One example of a technology is LY3410738 which is an oral medicine in development for the treatment of advanced haematological malignancies and is modified to have a substitution mutation in arginine 132 to make effective (NCT04603001; TRL 5).

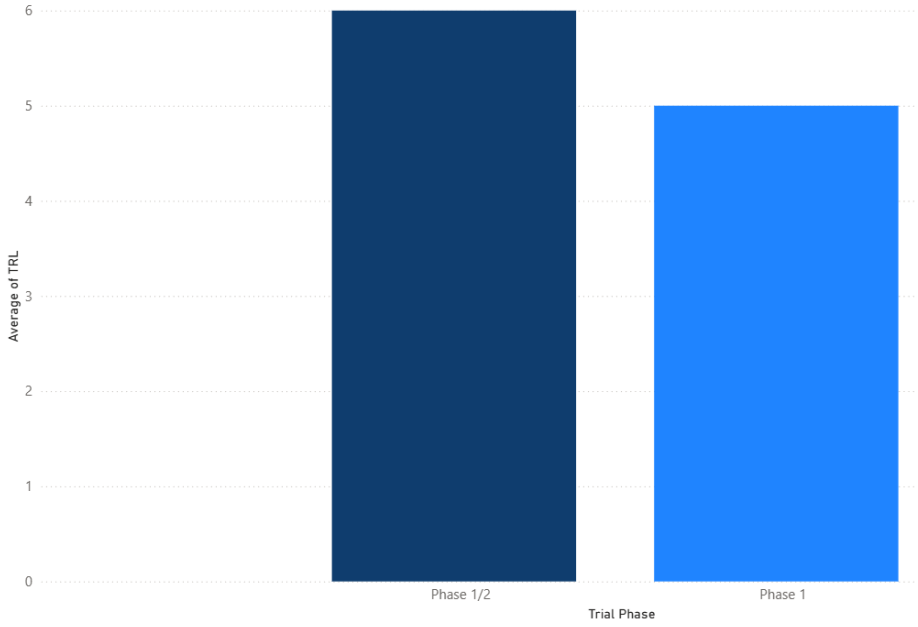

Figure 11 showing the average TRL for technologies in each phase of development in trials.

PubMed[20]

233 results were identified through searching PubMed for arginine: some relevant and recent examples include:

1. Arginine methylation is catalysed by protein arginine methyltransferases (PRMTs 1-9) in both the nucleus and cytoplasm and is thought to be involved in many disease processes. Since PRMT5 is frequently upregulated in many types of cancers, trials are ongoing for its use in solid tumours. PRMT4 inhibitors, such as TP-064 and EZM302, were developed and pre-clinically tested for multiple myeloma, where upregulation of PRMT4 was observed. These are given to alter the arginine within cells e.g. methylate and therefore alter the gene transcription.[43]
2. Abnormal autophagy is directly linked to the development of various diseases, particularly immune disorders, neurodegenerative conditions and tumours. Non-

20 https://pubmed.ncbi.nlm.nih.gov/?term=%28Arginine%29+AND+%28%28%222025%2F01%2F01%22%5BDate+-+Publication%5D+%3A+%223000%22%5BDate+-+Publication%5D%29%29&filter=dates.2025%2F1%2F1-3000%2F12%2F12&filter=pubt.review&sort=pubdate&sort_order=asc

histone methylation plays a pivotal role in the regulation of autophagy and its associated signalling pathways. Targeting non-histone methylation offers a promising strategy for therapeutic interventions in diseases related to autophagy dysfunction, such as cancer and neurodegenerative disorders.[44]

3. Researchers addressed low intra-tumoural L-arginine levels, which are known to limit PD-L1 antibody efficacy, by engineering E. coli Nissle 1917 to convert tumour-derived ammonia into L-arginine, boosting T-cell activity and tumour clearance in both solid tumours and leukaemia's. Additionally, CAR-T cells were modified to express arginine-synthesizing enzymes, enhancing their proliferation and tumour-killing ability in low-arginine environments without reducing cytotoxicity.[45]

EMBASE

15 results were identified through the searches on EMBASE. Some relevant examples include:

1. Bioengineered bovine papillomavirus L1 protein virus-like particle (VLP) vaccines are being investigated for use in the treatment of prostate cancer. Polyarginine/cysteine-tagged antigens are linked to the VLP by a reversible disulfide bond.[46]
2. An engineered cyclic arginine-glycine-aspartate modified tumour cell membrane-coated nanoreactor to improve the accuracy of chemotherapy in targeting hypoxic tumour cells.[47]
3. A novel single isoform of PEGylated human arginase has been created and found to exhibit potent cytotoxicity at sub-nM levels against cancer cell lines of breast, prostate or pancreatic origin.[48]

Links to most common applications

Application	Strength of link
Enzyme	7
Bacteria	4

Table 9 Application with a links to arginine

The two applications found with links to arginine were: enzyme (7) and bacteria (4). No trials were found in remit that included both key words 'arginine' and the unmet need of either 'enzyme' or 'bacteria'.

Herpesviridae

Clinicaltrials.gov[21]

[21] https://www.clinicaltrials.gov/search?term=herpesviridae&start=2020-01-

260 trials were identified from the search: 13 of those were terminated, 22 posted results, and 68 did not state the study phase. 52 trials met the inclusion criteria but 12 were duplicates and therefore removed. The remaining were assessed for TRL. 11 technologies had TRL5 (28%), 14 TRL6 (35%), six TRL7 (15%), and one TRL8 (2%); eight were TRL9 (20%) as they all examined an already marketed herpes zoster vaccine (Figure 12). The average TRL was 6.58. One example of a genetically engineered technology using Herpesviridae is T3011, which is a genetically engineered herpes simplex virus that is being used to treat bladder cancer (NCT06427291; TRL5).

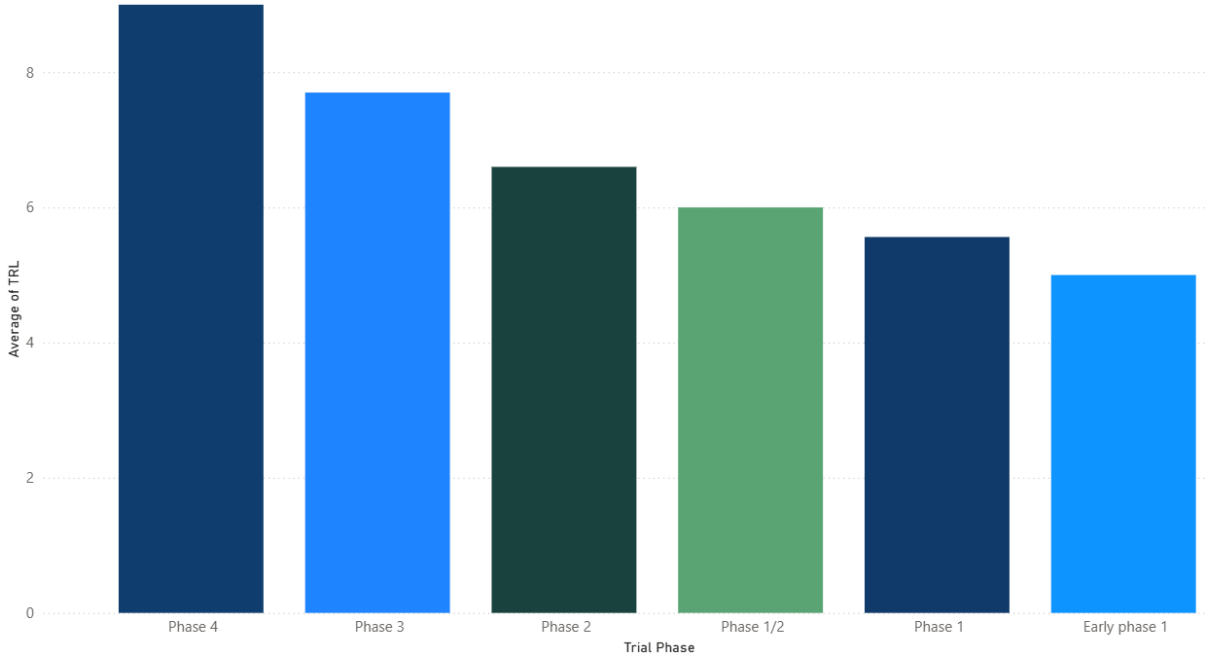

Figure 12 showing the average TRL for technologies in each phase of development in trials.

EMBASE

No papers were identified with this key word.

PubMed[22]

198 papers found were identified in our PubMed search for Herpesviridae. Some relevant examples include:

01_&aggFilters=phase:0%201%202%203%204,status:not%20rec%20act%20com

[22] https://pubmed.ncbi.nlm.nih.gov/?term=%28Herpesviridae%29+AND+%28%28%222025%2F01%2F01%22%5BDate+-+Publication%5D+%3A+%223000%22%5BDate+-+Publication%5D%29%29&filter=dates.2025%2F1%2F1-3000%2F12%2F12&filter=pubt.review&sort=pubdate&sort_order=asc

1. Kaposi's sarcoma-associated herpesvirus (KSHV) is an oncogenic gamma-herpesvirus that plays a major role in several human malignancies. KSHV expresses coding and noncoding RNAs which play crucial roles in modulating viral gene expression, immune evasion and intercellular communication. Targeting these RNA modifications could disrupt key viral processes, offering promising insights into KSHV pathogenesis and therapeutic interventions.[49]
2. Herpes Zoster (HZ). Recent studies suggest a potential association between HZ and the development of dementia, particularly Alzheimer's disease. Epidemiological evidence indicates that HZ infection, especially in individuals with central nervous system involvement, may increase the risk of dementia - therefore the novel recombinant Shingrix vaccine may be protective.[50]
3. The Epstein-Barr virus (EBV) has established lifelong persistent infection in about 95% of the adult population. The presence of EBV in tumour cells provides a unique advantage in targeting the viral genome, to develop anti-cancer therapeutics. Emerging technologies, such as CRISPR-based gene editing or activation, offer promising avenues for selective targeting of the EBV episome for anti-cancer therapy.[51]

Links to most common applications

Application	Strength of link
Immune	3

Table 10 Application with a link to Herpesviridae

The only application with a link to Herpesviridae was found to be 'immune', with a link strength of 3. All trials identified by combining these search terms together were found in the original trial search which resulted in a general TRL of 6.58.

Discussion

Methodology

This report used a novel methodology: first, a comprehensive bibliographic search was undertaken, the results from which were uploaded into the visualisation tool VOSviewer. Secondly, VOSviewer generated a keyword list which was downloaded into Excel. This list was used to categorise keywords into the "genetic engineering" category (or to the "therapeutics and drug delivery" or "tissues and medical devices" categories, which are the subjects of further reports), as a "non-specified new technology" or an application. The keyword list was refined, including creating a thesaurus to group keywords under a single term. The keyword list was used to create maps in VOSviewer, and then the most frequent and newest keywords were further analysed. Part of this further analysis involved linking technologies to an application; while this technique had limitations, it enabled proof of concept.

Methodology advantages

The advantage of this new method is that it is targeted and objective. The search was conducted in a relevant database using keywords developed from recent literature, ensuring a comprehensive dataset. If a more specific search was used, terms might be missed due to indexing or use of a synonym or alternative spelling, increasing the level of bias. This dataset was then analysed objectively, using pre-defined criteria to categorise the keywords found and then applying frequency and date filters.

This rigorous and objective approach ensured that the keywords found are those most likely to relate to game-changing technologies. It is a similar methodology that adopted by three previous papers, all published by the same research group (Fujii et al. 2022,[84] Takata et al. 2022,[85] and Otsuka et al. 2023).[86] All three apply bibliometric analyses to horizon scanning, in the fields of drug development related to T cell immune response; AI-based medical products; and 3D bio-printing, respectively. Our approach differs in three key aspects. First, these three papers each focus on one specific area whereas our approach starts much broader, taking in all of bioengineering and then identifying keywords to subsequently undergo in-depth analysis. Secondly, the other papers analyse articles rather than keywords. Finally, they use publication date in a time series approach to identify key milestones in the history of each field, whereas we use publication date to identify the newest keywords. Therefore, while these three papers confirm the validity of the overall approach, the differences in aim and approach mean that an exact replication of the method would not have been appropriate.

Methodology limitations

This was a horizon scan to identify technologies of interest rather than to perform evidence synthesis: further work would be required to investigate each in depth. For example, a relatively brief literature search identified a study into a microfluidic device that could successfully maintain human glioblastoma tissue[87], which could replace current preclinical models. However, since the study did not include terms relevant to bioengineering, it was not found by our initial search. Therefore, future projects that include deeper analysis could use the keywords to perform more intensive and comprehensive searches.

Since this is a new methodology, it will inevitably have limitations which should be acknowledged and can be worked on in the future. The first is that we restricted the search initially to one bibliographic database (Embase/OVID). However, this database is comprehensive;[88] and in addition Donthu et al. (2021)[89] suggested using just one database to minimise potential human error during format conversion and data cleaning. The search was carried out in English only; further work could explore the possibility of including other languages. Finally, only the clinicaltrials.gov registry was searched: future work could explore the use of other clinical trial registries.

We selected only the most frequent and newest keywords for further analysis; exclusion of the mid-range occurrences is acknowledged as a limitation as these could indicate translational technologies. However, selecting the top and newest keywords does present the advantage of being a repeatable method as these are defined points. Furthermore, analysis of the mid-range immediately presents the question of whereabouts the range should begin and end. In addition, the selected keywords provide a starting point for further searches into their application, rather than being presented as the game-changing technologies themselves: it is these searches that identify the latest publications regarding possible applications of the technology. Finally, the

searches for these keywords can easily be performed again to obtain updated information: either to monitor the progress of previously-identified technologies or to identify new ones.

The methodology used to identify links between technologies and unmet needs was experimental but demonstrated proof of concept. The main limitations concerned the searches for the keyword in Endnote: first, this library contained keywords from across the whole bioengineering project and therefore some that were identified were not relevant to therapeutics and drug delivery and may for example have related more to tissues and medical devices. However, the identified technologies are still likely to have strong links to unmet needs across the whole of bioengineering and thus should not be discounted. Secondly, the Endnote library was created in January 2025 from a search that spanned 2020-2025 and therefore the keywords represent only the body of work published at that time, more recent keywords would not be represented. Time constraints prevented the searches from being re-conducted. Future iterations of this method would build in time to re-run searches that are specific to the keyword. Thirdly, the analysis assumes that keywords represent technologies, and yet secondary searches showed that a technologies' primary identity was often something different, for example, a drug target or an outcome measure. Therefore, a high occurrence of a keyword did not necessarily reflect high occurrence of its use as a technology. For example, microRNA would not have yielded as many occurrences if only papers exploring microRNA as a technology were included. Thus, caution should be taken when making inferences from keyword occurrences, as the method served primarily as a means of identifying potential technologies for deeper analysis rather than providing a direct measure of their prevalence. Therefore, while this iteration of the method has limitations, their solutions are straightforward.

Findings and implications

CRISPR

CRISPR is a well-established technique used to edit/modify genes to correct mutations, inactivate genes, or insert new genetic material.[9] The diverse uses of CRSIPR were seen across the trials included, with a range of diseases and disorders represented such as sickle cell disease, lupus, and various cancers. Most of the technologies were found to be at TRL5-6 due to the high levels of phase 1 and 2 trials, and the most established were found to be at TRL7. This is likely due to CRISPR being used as a technique for many established drugs and vaccines on the market, such as Casgevy,[10] but reporting in trials often does not explain the gene editing process and therefore do not include the term CRISPR and do not appear in our search. Several technologies such as CTX001 (TRL7) and MT027 (TRL5) appeared several times in our results as they were being investigated for use across multiple diseases.

The bibliometric analysis resulted in lower number of results that could be included in the results, likely due to CRISPR being a general technique that is becoming widely used in lab-based study, animal studies, or genetically modifying plants to combat disease and increase yield. The literature showed several examples of CRISPR being used to combat antimicrobial

resistance through either phage therapy or the CRISPR-Cas13 system. CRISPR-Cas13 has been in development for some time, with a 2016 study by Abudayyeh et al. demonstrating that the ssRNA cleavage could restrict host bacteria growth.[52,53] Whilst phage therapy has also been in use since the 1930s, it has recently become more important in the field of genetic engineering and multidrug resistant bacteria due to increased need, high specificity and the new innovation of using phages to deliver CRSIPR-Cas3 to their bacteria hosts, shredding the bacterial DNA.[54,55]

CRISPR-Cas9 was used in several of the examples found across our bibliographic searches. The development of this method of genome editing earned the Nobel prize for chemistry in 2020 and has since been used to cure life-threatening diseases, make coronavirus detection tests, and even to modify human embryo cells with the consequent birth of babies carrying the introduced modifications.[56] CRISPR-Cas9 technologies are now also moving towards cancer treatments that could inactivate oncogenes which drive tumour growth, showing how the use of this technology is becoming more widespread across disease areas.[57] The terms found linked to CRISPR as applications were generally terms that relate to how the technology works such as 'gene' and 'plasmid', but terms such as 'liver' are reflected in some of the examples found such as CRISPR-Cas9 editing of donor liver grafts to reduce immunogenicity (NCT07053488 [TRL5]).

Patent disputes over CRISPR-Cas9 gene editing technology have highlighted a gap in international consistency in ownership of technologies such as this where they have been developed by multiple institutions in stages (Broad Institute MIT and UC Berkley each claiming ownership and the USA and EU granting it to different institutes). Fragmented ownership and licensing landscapes have shown the need for new licensing models to encourage open access and not to price out smaller companies.[58]

MicroRNA

The TRLs for this technology had a range of 5-7 with the majority (seven technologies) being TRL6. The included technologies were a low proportion of the results due to miRNAs commonly being uses as a biomarker in trials to see how well treatments are working, prognosis of disease, or in the initial diagnosis.[59] Examining the included trials shows a range of indications being studied. Cancer indications had the lowest TRL (5, 5 and 6), due to early phase 1 and phase 1/2 trials. Links to cancer related application words e.g. 'tumour growth' were stronger than most non-cancer applications, which could be an early signal of increased research into this area. Non-cancer indications had progressed slightly further, and indications included conditions such as epilepsy, amyotrophic lateral sclerosis and diabetic macular oedema. Only two of the identified technologies were being investigated in several trials.

Searches of the literature also showed a wide range of results with diseases such as osteoporosis, rheumatoid arthritis, multiple sclerosis and Alzheimer's disease. Many of the articles captured preclinical data. MiRNAs are crucial regulators of gene expression involved in various pathophysiological processes and can also modulate multiple pathways simultaneously. The ability to regulate a broad number of targets at once has led to issues regulating off target

effects/adverse events in clinical trials and has led to concerns about toxicity. Therefore, no miRNA-based products have reached the market yet and reflects the TRLs seen across trials.[60] MiRNA therapies have been found to suffer from several major challenges that other RNA-based therapies such as small interfering RNA (siRNA) and mRNA vaccines do not. They have been found to have toxicity, primarily inefficient delivery and have lower specificity that siRNA. Validation of targets is also time-consuming and expensive. Overcoming these challenges is difficult but advanced delivery systems such as nanoparticles mean that progress is still being made.[61]

Saccharomyces cerevisiae

Recombinant quadrivalent human papillomavirus (HPV) vaccines are widely administered across the UK to girls over the age of 9. The vaccine works using recombinant DNA technology to insert HPV genes into the DNA of *S. cerevisiae*. The vaccine has been found to be 95% effective in preventing cases of cervical cancer caused by HPV6, 11, 16 or 18.[62] Two technologies were found to have a TRL6: Sargramostim for Parkinson's disease and XP-DC for ovarian cancer. Sargramostim is a recombinant human granulocyte-macrophage colony-stimulating factor that is produced by using the *S. cerevisiae* expression system.[63] XP-DC is an autologous tumour lysate-loaded autologous XP-DC (cDC1)-based vaccine being investigated as a treatment for patients with ovarian cancer.[64] XP-DC refers to the genetically engineered strain of *S, cerevisiae* that is used in treatments, but it has been found that *S. cerevisiae* has a 'robust chassis' that can be altered so a wide variety of treatments and it can also be modified to be extremely fast growing.[65]

As *S. cerevisiae* is a common baker's yeast, many of the results for both clinical trials and literature were not relevant due to it being widely used in non-health sectors. The examples found in our literature review that we included covered a wide range of applications such as anticancer, antibacterial and antiosteoporosis therapeutics. One of the predominant model organisms used in bioengineering is *S. cerevisiae*. The most common use of this yeast is making it into a 'cell factory' to produce specific proteins within the body. The yeast is used as an engineering platform to build and manipulate DNA up to whole chromosomes. This has led to the ability to build plasmids at low cost and high throughout, leading to a highly diverse range of applications as seen in the technologies included in our research.[34] The broad nature of its use as a building block across a range of applications may also reflect the low number of key words linked to it with only 'transcription factor' and 'synthetase' found as common applications, both words relating to general genetic processes or proteins.

Staphylococcus epidermidis

For our least frequently occurring but newest keywords, *S. epidermidis* was identified and then searched, resulting in two trials that met our inclusion criteria. This bacterium is usually a non-harmful commensal bacteria found on the skin and is often found to help balance the epithelial microflora environment. The pathogen is now understood to be an important opportunistic

bacterium that results in high levels of infections during procedures such as medical device implantation. Infection with *S. epidermidis* is extremely difficult to treat due to the bacteria's ability to evade the immune system.[66] Two technologies were identified (ATR04-484 [TRL6], ATR12-351 [TRL5]) and both are investigational live biotherapeutic products that uses an engineered strain of *S. epidermidis*. Most strains of *S. epidermidis* have a strong restriction barrier that hinders the exchange of DNA. This barrier can be overcome, but means that *S. epidermidis* strains are more difficult to work with than the more commonly used *S. aureus* which may be why this key word was found in such low levels.[67]

The low number of clinical trial results was mirrored within the literature search, as only two papers were identified across both databases. One of the examples discussed using *S. epidermidis* to create extracellular vesicles to mitigate inflammation and aging within the skin.[41] Extracellular vesicles have been extensively used for drug delivery but in recent years the endogenous method based on genetic engineering has gained significant attention. Genetically engineered loaded extracellular vesicles have been shown to transfer therapeutically relevant active compounds into target cells *in vitro*, meaning they have a strong foundation to be considered as potential therapeutic candidates in future development.[68]

Arginine

Whilst 241 trials appeared in the search for arginine, only five of these fell within the inclusion criteria. Of these five technologies, two had Market Access in the UK, meaning they were TRL9: an inactivated polio vaccine and pegzilarginase, which is an enzyme produced by recombinant DNA technology that is administered as enzyme replacement therapy for the treatment of arginase-1 deficiency (hyperargininaemia).[69] LY3410738 appeared twice in the results, being investigated for a range of blood cancers (acute myeloid leukaemia, myelodysplastic syndromes, chronic myeloid leukaemia) and cholangiocarcinoma. LY3410738 targets mutations in the IDH1 and 2 genes found in some cancers. These mutations are commonly found are arginine locations e.g. arginine residue 132, 140 or 172 and this causes oncogenic affects which can be mediated by using this as a target.[70] Another technology identified in the clinical trials was a pooled mutant KRAS-targeted long peptide vaccine where synthetic peptides are created as a platform for the neoantigen vaccines using genetic engineering techniques for delivery such as viral vectors to target arginine mutations in the KRAS-gene within cancers such as non-small cell lung cancer.[71,72]

The literature search found several examples of arginine used within genetic engineering. Relevant examples mainly focused on cancer treatments. Within genetic engineering, arginine is often discussed due to modifications at arginine sites within genes. A key post-translational modification of DNA is carried out by protein arginine methyltransferases (PRMTs) that either directly methylate DNA repair proteins or help regulate their transcription, RNA splicing, protein stability, interaction with partners, enzymatic activities, and localisation.[73] The methylation of arginine is increasingly associated with cancer progression making the development of PRMT inhibitors important. PRMT5 has been found to be highly upregulated

in various cancers offering a promising target for researchers, with minimal side effects for patients.[74]

Herpesviridae

Clinical trials included from our search included many technologies with market access such as the recombinant herpes zoster vaccine and the live attenuated vaccine. Each of these uses genetic engineering to either create a weakened version of the pathogen through targeted gene deletion/modification or, in the case of recombinant vaccines, use a bacteria or yeast inserted with pathogen DNA to produce the active compounds for the vaccine.[75] Vaccines were the predominant technology found in the clinical trials, accounting for 17 unique technologies. Herpes zoster, also known as shingles, results from the reactivation of the varicella-zoster virus: approximately 95% of adults aged 50+ have been infected with this, giving a lifetime herpes zoster risk of 30%. This makes study in this area of key interest to limit the worldwide health burden as the technology could have a global impact on health. The potential to use the already developed vaccine platforms in other areas is being investigated as the infrastructure may already be in place for fast implementation. This may be reflected in the TRL average of 6.58 showing that a significant number of technologies are in a later stage of development in comparison to other technologies investigated.[76] One of the non-herpes treating/prevention technologies identified in the trial search was T3011 (TRL6) for bladder cancer. T3011 is a genetically engineered oncolytic herpes simplex virus type 1 expressing the human immunostimulating cytokine IL-12 and an antibody directed against the negative immunoregulatory human cell receptor PD-1, with potential immune checkpoint inhibitory and antineoplastic activities.[77]

The literature results differed from the clinical trials in that they were focused on non-herpes treatments such as cancers and other conditions. Herpesviridae refers to the family of DNA herpesviruses and these have more recently been found to have a wide number of applications. The herpes simplex virus has been used as a vector for gene delivery, and has a natural neurotropism which has led to investigation in this area.[78] One of the most promising new oncolytic therapies containing modified Herpes simplex virus is RP2 which has been designed to target and kill cancer cells with high specificity. In RP2 the herpesvirus acts as a multifaceted gene therapy vector and induces production of human granulocyte-macrophage colony stimulating factor which promotes anti-tumour immunity.[79] This builds on similar gene therapies that use the herpesvirus such as Imlygic which has market access in the UK for the treatment of unresectable melanoma.[80,81]

Conclusion and implications

This report discusses six genetic engineering key words identified in our research. 10 keyword clusters were identified overall, not only showing the breadth of genetic engineering research but also suggesting that gene editing is becoming more common in research overall as techniques and knowledge grow. Most identified technologies were found to be of TRLs 5-7,

suggesting strong preclinical and early clinical activity. This may suggest difficulties in translating these technologies into licensed products which can occur due to high research costs, difficulties scaling often personalised medicine for wider markets, and regulatory complexity seen with genetically engineered products.

CRISPR was found to be the most commonly occurring technology investigated but no trials were found to be TRL8 or higher. This is likely because the search dates excluded trials where the technology has subsequently reached the market, therefore this data gives a snapshot into current research. Additionally, information in clinical trials is often vague which may mean that CRISPR or other technologies mentioned in the report were missed in the data due to unclear reporting if no literature was available for clarification. Strong links were seen between CRISPR and genes/plasmids, but not disease-specific terms, which might suggest many applications are still experimental and treatments are not yet widely established or specialised. miRNA-based therapies show stronger links to diseases or tissue key words such as 'tumour growth' and 'nervous system inflammation', showing that applications are becoming more focused though challenges in delivery and specificity remain. *S. cerevisiae* was the most mature technology, possibly due to the large number of marketed recombinant vaccines that modify this yeast for production. Recombinant vaccines are well established, making the higher numbers expected, but new innovations were also seen.

Research into *S. epidermidis* for therapeutic use was found to have limited trials and published literature with limited TRL progression indicating that this is at early stages. Arginine-related studies showed innovations such as synthetic biology to enhance CAR-T therapy and tumour metabolism, but advances in this area would be hard to quantify because arginine is an amino acid that plays a crucial role in DNA replication and repair, making it involved in many aspects of genetically engineered technologies. Herpesviridae-based technologies were found to be of a similar maturity as *S. cerevisiae* in the sense that both had several recombinant vaccines that were licensed, making this keyword differ from the other least frequently occurring words analysed. Links to applications for this group of keywords were found to vague and not disease area based, again highlighting that in current research these are not widely studied.

To ensure these technologies reach patients as soon as available key regulatory and ethical hurdles must be addressed. Key issues include demonstrating long-term safety and durability of effect for gene-editing and vector-based therapies, managing off-target affects and risks to patients, and developing appropriate frameworks to account for a rapidly evolving landscape. Ethical considerations also need to be addressed through transparent reporting and public engagement where possible.

Overall, we can see clear opportunities for the integration of each of these technologies into healthcare pathways. Genetic engineering is developing rapidly but with technologies still in earlier stages of readiness there is opportunity to develop pathways and frameworks to support upcoming innovations. Clear, flexible licensing and patent pathways would help to ensure future collaborations and enhance innovations, helping to achieve faster and clear market access routes so technologies can reach patients more efficiently.

Other information

The raw data used in this report can be made available on reasonable request.

Appendix A: keywords by cluster

The analysis of each cluster is shown in the following sections. The most frequent keywords are highlighted in blue, and the least frequent new keywords highlighted in orange. A total of 205 keywords were extracted.

Cluster 1

Keyword	Links	Total link strength	Occurrences	Average publication date
Microrna	44	130	111	2022.30
Small interfering rna	36	93	48	2022.38
Recombinant protein	32	56	41	2021.95
Complementary dna	19	22	11	2022.55
Ribosome rna	6	8	7	2021.71
Ubiquitination	10	14	7	2022.57
Signal peptide	5	6	6	2021.83
In situ hybridization	6	7	6	2022.00
Transcription factor nrf2	8	12	6	2022.17
RNA processing	11	15	6	2022.83
Plasmid vector	10	13	5	2021.40
Knockout gene	10	11	5	2021.60
RNA binding protein	10	14	5	2022.00
Muscle regeneration	4	6	5	2022.20
Herpesviridae	8	8	5	2023.40

Cluster 2

Keyword	Links	Total link strength	Occurrences	Average publication date
Gene	41	97	83	2022.06
Amino terminal sequence	24	47	40	2021.43
Carboxy terminal sequence	21	41	32	2021.63
Chimera	19	23	26	2022.08

Polyketide synthase	10	18	17	2021.53
Protein p53	11	15	12	2021.92
Virion	4	4	7	2022.57
Streptavidin	13	14	6	2022.67
Arginine	5	6	5	2023.40
Maleimide	5	7	5	2022.00
Methionine	3	3	5	2021.00

Cluster 3

Keyword	Links	Total link strength	Occurrences	Average publication date
Optogenetics	12	15	39	2021.54
Pseudomonas putida	20	30	16	2021.69
Komagataella pastoris	12	20	15	2021.67
Protein conformation	4	4	11	2022.00
Caenorhabditis elegans	13	17	9	2022.33
Pseudomonas fluorescens	4	6	7	2021.43
Transgenic organism	8	8	7	2022.29
Chaperone	5	6	6	2022.17
Transforming growth factor beta1	1	1	6	2021.67
Glutathione	5	6	5	2022.00

Cluster 4

Keyword	Links	Total link strength	Occurrences	Average publication date
Nuclear reprogramming	19	29	29	2021.69
Gene delivery system	14	23	25	2021.72

Lipid nanoparticle	15	27	23	2022.74
Ultracentrifugation	11	20	17	2022.47
Lentivirus vector	17	19	14	2021.21
Transposon	11	13	12	2022.00
Recombinant plasmid	6	7	7	2021.57
Transcription factor nanog	3	4	6	2021.00
Protein RNA binding	8	8	5	2022.20
Tumor suppressor gene	3	6	5	2021.60

Cluster 5

Keyword	Links	Total link strength	Occurrences	Average publication date
Crispr	58	137	135	2021.89
Saccharomyces cerevisiae	35	98	98	2021.67
Yarrowia lipolytica	8	19	22	2021.82
Corynebacterium glutamicum	13	27	20	2021.35
Guide RNA	15	26	10	2022.20
Agrobacterium tumefaciens	12	18	9	2021.67
Phenylalanine	7	9	6	2021.33
Recombinant DNA technology	9	9	6	2021.83
Squalene synthase	7	13	6	2022.83
Synthetic dna	6	6	6	2022.17

Cluster 6

Keyword	Links	Total link strength	Occurrences	Average publication date
Lactococcus lactis	21	36	26	2021.65
Polyethylene terephthalate	3	3	11	2022.36
Horizontal gene transfer	7	8	10	2022.20
Lactobacillus plantarum	13	17	10	2021.80

Streptococcus pneumoniae	9	10	7	2021.86
Enterococcus	11	13	6	2021.67
Synechococcus elongatus	2	2	6	2021.83
Streptococcus agalactiae	7	10	5	2021.60
Bifidobacterium longum	5	6	5	2021.40
Streptomyces albus	7	8	5	2020.60

Cluster 7

Keyword	Links	Total link strength	Occurrences	Average publication date
Gamma interferon	25	63	53	2021.83
CAR-t	25	46	47	2021.77
CD8+ t lymphocyte	21	43	42	2021.79
Electroporation	27	61	39	2022.31
Molecular probe	3	3	6	2021.67
Megakaryocyte	4	4	5	2021.80
Transferrin	1	1	5	2021.40

Cluster 8

Keyword	Links	Total link strength	Occurrences	Average publication date
Genetic transfection	26	59	49	2021.86
Cell free system	5	6	16	2021.75
Transgenic microorganism	5	6	12	2021.92
Plasmid dna	7	9	7	2022.43
Restriction endonuclease	6	7	6	2022.17
Stable expression	3	3	5	2022.20
Marker gene	7	7	5	2021.40

Cluster 9

Keyword	Links	Total link strength	Occurrences	Average publication date
Heterologous expression	19	48	36	2021.81
Transcription factor runx2	8	10	19	2022.21
Beta actin	3	3	6	2021.17
Gene construct	5	6	6	2021.67
Notch receptor	5	5	5	2020.80

Appendix B: protocol for translating trial phase into TRL

1. Read trial to make sure it is an application of the keyword
2. Read trial to make sure it is relevant to the specific arm of bioeng (eg tissues and medical devices)
3. Briefly read the trial and see if the technology is named
4. If it is, search for the name on Google:
    a. If it is on market TRL9
    b. If it has obtained FDA/EMA approval, TRL8
    c. If it has submitted FDA/EMA approval, TRL7

If not named, for trials with phase: (https://uhsf.nl/wp-content/uploads/2020/02/TRL_overview_UHSF_version20200206.pdf)

5. Take trial phase/status. If a double-phase ie phase 1/2, take the higher phase
    a. P1 ongoing/early phase 1 complete, TRL5
    b. P1 complete/P2 ongoing, TRL6
    c. P2 complete/P3 ongoing, TRL7
    d. P3 complete/P4 ongoing, TRL8

For trials without phase: https://www.ukri.org/wp-content/uploads/2022/01/EPSRC-11012022-Technologyreadinesslevelsfrombasicresearchtoadoptionanddiffusion.pdf

6. Read trial: search for word “safe” or “safety”
    a. If safety trial is ongoing (including recruiting and not yet recruiting), TRL5
    b. If safety trial is complete, TRL6
    c. If secondary trial ongoing (search “efficacy”), TRL6
    d. If secondary trial complete, TRL7

NB for a product already on the market for a different indication to the one on test, note this. Eg Technology X already marketed for cancer but in ongoing P2 for diabetes would be TRL9 for cancer and TRL6 for diabetes. If for comparison of two marketed products, TRL9.

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