厚生労働行政推進調査事業費
次世代バイオ医薬品等の革新的な医薬品創出に向けた環境整備に関する研究
分担研究報告書
「バイオ医薬品、再生医療等製品の開発促進に係る諸外国のエコシステム調査」

研究代表者・分担研究者
坂巻　弘之　（神奈川県立保健福祉大学　大学院ヘルスイノベーション研究科　教授）

研究協力者
内田　和久　（神戸大学大学院　科学技術イノベーション研究科　教授）

梶原　大介　（Cytiva　エンタープライズソリューション部　部長）

要旨

バイオ医薬品、再生医療等製品の開発促進に係るエコシステム、人材育成組織の先進事例の調査を行うこととし、英国 Cell and Gene Therapy Catapult（CGT Catapult）およびアイルランド National Institute for Bioprocessing Research & Training（NIBRT）の現地訪問を行った。CGT Catapult は、細胞治療・遺伝子治療の研究成果を商業化へ橋渡しする組織として設立され、企業に対し、臨床・プロセス開発・製造・規制等に関す専門知識の提供が行われている。早期に医療経済についてもアドバイスが行われている。NIBRT は、バイオプロダクション関連の機能を統合して国立の研究所としてスタートしたが、バイオ関連製品の教育トレーニング、細胞エンジニアリング等の研究事業を実施している。もともと国立研究所であるが、世界的なバイオ医薬品開発の活発化もあって、独自の事業収入も拡大し、英国の EU 離脱なども追い風となり。組織としても拡大している。

A 目的と方法

バイオ医薬品、再生医療等製品の開発促進に係るエコシステム、人材育成組織の先進事例の調査を行うこととし、英国 Cell and Gene Therapy Catapult（以下 CGT Catapult）およびアイルランド National Institute for Bioprocessing Research & Training（以下 NIBRT）の現地訪問を行った。
訪問日および担当者は以下の通りである。

① CGT Catapult

2020 年 1 月 8 日
Ms. Shirley Lam
Michael Bennett
(Business Development Manager – Asia)
12th Floor Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT
http://ct.catapult.org.uk

② NIBRT

2020 年 1 月 10 日
Killian O'Driscoll（Director of Projects）
Fosters Avenue Mount Merrion Blackrock Co. Dublin A94 X099
https://www.nibrt.ie/

B 結果と考察

1. CGT Catapult

CGT Catapult は、英国政府の研究資金助成機関である Innovative UK によって 2012 年に設立された独立研究機関であり、再生・細胞医療分野では世界トップレベルの産業化促進機構とされる。再生医療への支援を行うため、2016 年に Cell Therapy Catapult から Cell and Gene Therapy Catapult へ名称変更して

いる。英国が細胞・遺伝子治療におけるグローバルリーダーとなって、企業が最先端の治療を開発し迅速かつ効率的・効果的に患者に提供できるようにすることを目指し、臨床・プロセス開発・製造・規制に加え、医療経済・マーケットアクセスに関する専門知識の提供等により、多くの企業と協業している。

ネットワークを構築し先端治療の患者へのアクセスを加速するための組織として、Advanced Therapy Treatment Centres (ATTC)が Innovate UK の投資により、2017 年に設立されているが、この組織のプロジェクトの調整と支援を CGT カタパルトが中心となって担っている。

施設規模としては、(開発センター／製造センター)ロンドンの Guy's Hospital 内に、UK の CGT Catapult センターには、Development Lab と Manufacturing Center が存在する。Manufacturing Center は、2018 年にオープンし、7,200m^{2}の敷地面積を有し、GMP に準拠した大規模製造センターを開設しており、研究開発だけでなく製造上の課題にも対応できる。

CGT Catapult は、Bio の技術力をコアに、以下の 3 本の柱で仕事をしている。Hospital base のネットワークを通じてコラボレーションを進めている。

- Core
  - Key challenges and barriers
  - A unique technical capability
  - Industry & research advisory groups
  - Demonstration projects
  - Disseminate to industry
- Commercial
  - Access to unique facilities & expertise
  - Develop & demonstrate at scale
  - Reduce risk of implementation
  - Direct contracts for projects
  - Easy access for SMEs
- CR&D
  - Innovation in collaborations
  - Bring together customers, SME's & blue-chip companies
  - Technical & management resource
  - Partners in Projects (IUK & EU)
  - Expertise at unlocking funding

CGT Catapult 自身は Products には責任を持たず、そこはコラボレーターがリードする。コラボレーション含めて、70 名の PD 研究者を抱え、CGT Catapult の研究者が PD を行い、GMP はクライアントが CGT Catapult 内の CPC を使用して実施する。

CGT Catapult では、Risk Sharing/Cost Sharing のビジネスモデルをポリシーとしており、12 の CPC の貸し出しや近隣大学とのコラボレーション(学生の学位取得プログラム、共同研究)などを実施している。

CGT Catapult の概要ならびにビジネスポリシーに関する資料を**添付資料1**として添付した。

再生医療等製品は、高価格の製品も多く上市されている。CGT Catapult では、探索段階から、医療経済・マーケットアクセスの専門家が、企業へのコンサルティングも行っている。新医療技術に対する各国の公的制度での償還(カバー)は、EU 各国それぞれの判断を行うため、欧州の主たる国についての制度に対応できるアドバイスも行っている。経済評価に関する概要ならびに実施事例について**添付資料 2** として添付した。

CGT Catapult の Key は大学、企業とのネットワークによる専門性を持つ人材の確保と、それらの人材を有効に活用できるレンタルファシリティーにあると考えられる。地域の大学教育に貢献する形をとりつつ、逆に Cell & Gene Therapy の開発、製造プロセスに精通したノウハウと人材を確保する。それらの人材の強みを生かして、人材とキャパシティにペインポイントを抱える、バイオテックらに GMP ファシリティと人材の貸し出しを行う。それを通じて、さらに CGT Catapult にもノウハウがたまる仕組みである。これがうまく回れば、

まさに効果的なエコシステムを構築可能であると感がられる。一方、CGT Catapult の Key は大学、企業とのネットワークによる専門性を持つ人材の確保と、それらの人材を有効に活用できるレンタルファシリティーにあると考えられる。地域の大学教育に貢献する形をとりつつ、逆に Cell & Gene Therapy の開発、製造プロセスに精通したノウハウと人材を確保する。それらの人材の強みを生かして、人材とキャパシティにペインポイントを抱える、バイオテックらに GMP ファシリティと人材の貸し出しを行う。それを通じて、さらに CGT Catapult にもノウハウがたまる仕組みであり、これにより効果的なエコシステムを構築が可能であると考えられた。

2. NIBRT

2011 年にアイルランド内の 4 つの大学の競合していたバイオプロダクション関連の機能を統合して、機能を強化もかねて、国立の研究所としてスタートした。設備は経産省系の資金でアイルランド国内にバイオ関係の投資を増やす目的で、バイオプロセスの生産の研修背引用施設(6500 ㎡)として設立している。年間、社会人、学生など総人数では 4300 名の教育を実施している。各大学と N|BRT とは、単位に相互互換あるので、バイオ関連を目指す学生の育成にも効果的である。

事業収入は、教育トレーニング講習費、リサーチ分野の研究資金、政府補助が 3 つの柱で、合わせて 7M ユーロ/年とのこと(ちょうどわが国の般社団法人バイオロジクス研究・トレーニングセンターBCRET の 10 倍程度の事業規模。年間受講者数やスタッフの数もちょうど 10 倍の規模になる)。

設備は、ステンレス培養槽で 150L、シングルユースで 200L 程度のアップストリームとそれに対応するダウンストリームおよび製剤の無菌充填設備を用いて各種のハンズオントレーニングを実施する。

スタッフ数は現在、99 名とのことであり、このうち、教育トレーニングに係るのは約 25 名である。研究担当も含めて、フルタイム職員とパートタイム職員が混在している。スタッフは、新卒をとることもあるが、インダストリーで経験したメンバーを数年雇用し、また、インダストリーに返していくといった、雇用の循環の仕組みが出来上がっている。

2019 年は Cell & Gene Therapy や Pharma4.0 のような新規分野のプログラムがロンチされたが、こういった新規分野は、NIBRT 単独では行わず、それぞれの分野で強みを発揮する組織と連携して、共同で教材を開発する。

リサーチ分野に関しては、
Cell Biology & Engineering,
Bioinformatics & Data Analytics,
Bio Analytics,
Advanced Manufacturing
の分野の研究を行っており、この研究者もフルタイム職員だったり、他大学とのパートタイム兼任だったりする。米国のフィラデルフィラに The Jefferson Institute と共同で、The Jefferson Institute for Bioprocessing (JIB)を 2019 年 5 月に開設した。JIB では NIBRT と同様に模擬的なプロセス施設を持っており、インダストリー向けだけでなく、FDA への教育も開始した。NIBRT 概要のスライドを**添付資料3**として添付した。

NIBRT での教育トレーニングでの実習では、実習手順や実習操作自体は、実際の動きと同様に行うことにはこだわるが、実際の抗体発現細胞を使った培養や精製を行わないのが特徴である。抗体発現株を培養する培地コストがかかったり、Protein A といった樹脂が高価であったりするため、実習のコスト低減の

ためには、実サンプルは使わない。GE のシングルユース 200L までの装置をそろえた GE-NIBRT の共同施設はそれほど大きなものではない。70 ㎡程度の実験室で対応していた。ここでも、実際の抗体細胞を使ったりするわけではなく、あくまでも、手順、操作の習得にフォーカスしていた。

NIBRT 設立以降、順調に発展していると考えられる。主たるトレーニングや研究に加え、具体的には GE とのコラボレーションが始まり、E-ラーニングなどが充実している。スタッフも増え、予算規模も年間 7M ユーロ/年に達している。もともとは 100%政府資金で運営されていたが、現時点では 10%程度(邦貨で 7000 万円程度)となっており、独自のビジネスが順調に拡大していることを裏付けている。NIBRT の事業が延びる理由はいくつかあるが、"BREXIT"を好機ととらえている。アイルランド自体が UK の欧州離脱により欧州内で唯一の英語国家になり、英語でコミュニケーションをとる欧州のコミュニティーからの事業の集中を期待していると感じられた。

アイルランド全体での、バイオロジクス産業の市場は 2009 年から 2019 年の間に、22 件の製造サイトへの投資があり、金額では 1 兆円規模(10B $)の伸びで、1 万人の雇用が創出された。その中でも、WuXi Biotech の投資が 325 億円進出中の企業で最も多く(バイオ生産設備では世界でも最大級)、注目される。

グローバルに、NIBRT のパートナーを探しているとのことである。E-ラーニングに関しては、バイオ企業の初級者レベルの内容であるが、現在 6 種のプログラムで、各 45 分で 99 ユーロ、現在、英語バージョンのみであることから、今後、BCRET と連携などにより、日本語の翻訳バージョンを作成すといった共同事業の検討も考えられる。

C. 健康危険情報

該当しない。

D. 研究発表

1. 論文発表

未実施。

2. 学会発表

未実施。

E. 知的財産権の出願・登録状況

(予定を含む。)

1. 特許取得

予定なし。

2. 実用新案登録

予定なし。

3. その他

予定なし。

F. 添付資料(スライド)

1. Introduction to the Cell and Gene Therapy Catapult
2. The Health Economics & Market Access function of the CGT Catapult
3. Welcome to NIBRT

添付資料１　引用・複写を禁ずる。

CATAPULT
Cell and Gene Therapy

Introduction to the Cell and Gene Therapy Catapult

About us

- Part of a **world-leading network** of technology and innovation centres
- Provide access to unique technical **facilities** and **expertise** to help adopt, develop and exploit innovations
- **Bridge the gap** between businesses and academic research
- Established by Innovate UK as a **not-for profit**, independent centre

It is our vision for the **UK** to be **a global leader** in the development, delivery and commercialisation of cell and gene therapies.

Where **businesses can start, grow and confidently develop** advanced therapies, delivering them to patients rapidly and effectively.

Summary:

Accelerate	Complement	Innovate	Facilitate
the commercialisation of innovations from research	industry and academia with unique technical facilities and expertise	in collaboration with academia and industry	operating in UK as a global centre; working with Government, the NHS and international regulators

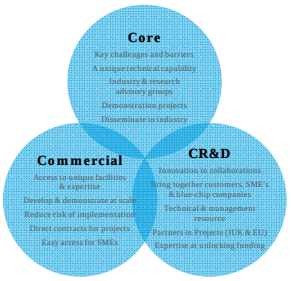
Development laboratories
- 1200m² purpose built centre
- Analytical characterisation
- Process development
- Viral vector

Manufacturing centre
- 7000m² manufacturing centre designed specifically for cell and gene therapies
- 12 segregated large clean room modules
- Secure supported collaboration model
- Centre of a cell and gene therapy cluster

Cell and gene therapy specialists (>180)

Industrialisation	Regulatory and clinical development	Engagement
- Process development - Analytical development - Manufacturing systems - Supply chain	- Regulatory - Non clinical safety - Clinical delivery - Programme management	- Collaboration formation - Intellectual property and patent - Health economics - Reimbursement

How do we work?



Strategic roadmap

2012 – 2017	2018	2023	2025	2035
Expertise	Commercialisation of research	World leading research & translation ecosystem	Global industry **$16bn**	Global industry **$80bn**
	Non viral gene delivery and gene editing			
Facilities	Industrialising viral vector gene delivery systems	Globally attractive research, development & manufacturing industry		
	Industrialising ATMP manufacture			
Capabilities	Large scale manufacture and supply		UK 4,000 jobs **£2bn industry**	UK 18,000 jobs **£10bn industry**
	Clinical adoption and reimbursement	World leading NHS clinical & reimbursement practice		
Technologies	Regulatory advantage	UK Exports	Productivity: Average GVA **£104,000 per employee**	
	Environment shaping: research, industry and policy engagement			

Cell and Gene Therapy Catapult manufacturing centre

Walk in infrastructure

The centre provides access to the expertise, skills, facilities and equipment as the stepping stone needed for organisations to develop new technologies and systems for large scale manufacturing.

- Quality control
- Qualified persons
- Operating policies
- Warehouse management
- Development assistance

Managed warehouse with delivery to your manufacturing space

Flexible quality control options

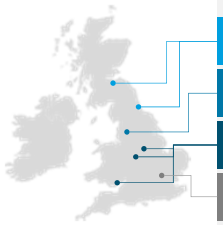
Manufacturing Centre

ATTC
Advanced Therapy Treatment Centres

Clinical adoption and reimbursement

Demonstrating proof of market through rapid clinical adoption and reimbursement

Coordinating the Innovate UK funded network of Advance Therapy Treatment Centres which will act as pathfinders for future adoption



- **Northern Alliance Advanced Therapies Treatment Centre**
- **iMATCH - Manchester Advanced Therapy Centre Hub**
- **MW-ATTC - Midlands & Wales Advanced Therapy Treatment Centre**
- **CGT Catapult manufacturing centre**

Creating easily run and ready to use systems and solutions that can be rolled out to other NHS centres, increasing patient access to ATMPs.

CATAPULT
Cell and Gene Therapy

12th Floor Tower Wing
Guy's Hospital
Great Maze Pond
London SE1 9RT

info@ct.catapult.org.uk
ct.catapult.org.uk
Twitter: @CGTCatapult

Cell and Gene Therapy Catapult is committed to ensuring high standards of research integrity and research best practice in the activities we carry out. We subscribe to the principles described in the UK concordat to support research integrity.

We work with Innovate UK

添付資料2　引用・複写を禁ずる。

The CGT Catapult's Health Economics and Market Access (HE&MA) team provides strategic support tailored to the needs of ATMP developers

The team	• Seasoned HE&MA professionals with prior **experience from senior roles with the industry and health technology assessment (HTA) bodies**
The expertise	• Numerous projects across **different cell and gene therapies,** at **different stages of development,** across a **variety of therapeutic areas**, including: • Oncology, ophthalmic diseases, musculoskeletal disorders, solid organ transplantation immunosuppression, cardiovascular disease, respiratory disease, metabolic disease, liver disease, infectious disease, Parkinson's, haemophilia, and haemoglobinopathies

- We have refined traditional HE&MA frameworks to address the unique challenges of ATMPs
- We are working with payers across European and North American markets to develop and shape how they reimburse cell and gene therapies
  - We leverage these relationships in developing pricing and reimbursement strategies
- We have access to all the other expert teams within CGT Catapult and a track record in working seamlessly to deliver multifunctional projects

Our HE&MA offering differs according to the development stage of a therapy

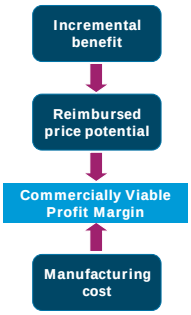
(Pre-clinical) Shaping early development	*(Pre-pivotal)* Opportunity optimisation	*(Pre-launch)* Tactical launch preparations

• Identify target patient population of greatest commercial potential
• Define the parameters of commercial viability and inform clinical and manufacturing strategy accordingly
	• Define the interrelationship between value story, reimbursed price potential and corresponding evidence requirements
	• Inform the evidence generation plan accordingly
		• Develop approaches to address
		  o Data uncertainty
		  o Healthcare system affordability
		  o Infrastructure and treatment pathway constraints
		• ...in addition to tactical pre-launch preperations that apply to all pharmaceuticals

LAUNCH

High manufacturing and delivery costs necessitate earlier consideration of reimbursement matters for ATMPs

- Majority of ATMPs are expensive to manufacture, administer and supply
- ATMPs therefore need to deliver a substantial incremental benefit (over existing therapies) in order to ensure a commercially viable profit margin
- Commercial risk mitigation focuses on:
  - Maximising incremental benefit
  - Minimising manufacturing costs
  - Reducing healthcare costs associated with the delivery of the novel therapy
- Accounting for reimbursement earlier and informing ATMP R&D strategy accordingly, is of priority...
  - ...and of even greater priority for those ATMPs qualifying for accelerated regulatory pathways



Failing to consider reimbursement matters prior to starting clinical development increases commercial risk

(Pre-clinical) Shaping early development → *(Pre-pivotal)* Opportunity optimisation → *(Pre-launch)* Tactical pre-launch preparations → LAUNCH

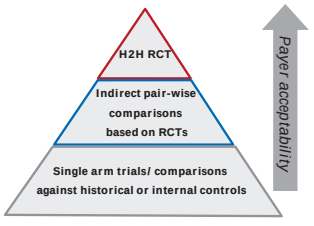
Commercial risk-minimisation in early ATMP development should identify:

- The headroom for innovation in the target indication/ therapeutic position to identify
  - The extent to which target indication can accommodate high-cost therapies
  - The target patient group with the greatest commercial potential (in the absence of clinical data)
- The value-maximising clinical, economic and humanistic outcomes
  - In order to inform the development of the early Target Product Profile (TPP) and evidence generation plan
- The interrelationship between therapy benefits and reimbursed price potential in order to define:
  - Product performance and manufacturing cost thresholds for commercial viability
  - 'Go'/'no-go' criteria for stage-gate decision-making across consecutive stages of development
- Inform clinical and manufacturing strategy accordingly

Clinical, regulatory and commercial considerations often necessitate a clinical development programme for ATMPs that payers find challenging

Common data challenges for ATMPs:

- Potential for a cure but lack of long-term data at launch
- Weak comparative effectiveness data vs. the standard of care (SOC) due to one or more of the following:
  - Head-to head (H2H) comparative data against the standard of care is not available
  - Randomised controlled trials (RCTs) not feasible, which limits prospect for indirect comparisons
  - Meaningful comparative data from single arm trials can not be generated due to e.g. limitations with the historical control data, the natural history of disease is not well known, or the patient population is heterogeneous
  - Small trials limit statistical significance of outcomes measured
  - Measuring only surrogate outcomes rather than hard clinical outcomes (risk for overestimation of benefit as per: *NICE Regenerative Medicine Study, 2016*)
  - No comparable treatment or outcome measures are available



Given the evidence generation challenges with ATMPs, it is important to engage with market access stakeholders early

(Pre-Clinical) Shaping early development → (Pre-pivotal) Opportunity optimisation → (Pre-launch) Tactical pre-launch preparations → LAUNCH

There are different options for engaging with key market access stakeholders:

- Centralised at national level: Parallel Consultation with EMA and European HTA bodies
- Decentralised at national level: Individual HTA bodies in different countries
- Decentralised at national, regional and local level (traditional payer research)

The objective of engaging with market access stakeholders is to identify the evidence that optimises reimbursement potential

(Pre-clinical) Shaping early development → (Pre-pivotal) Opportunity optimisation → (Pre-launch) Tactical pre-launch preparations → LAUNCH

Optimising the evidence-generation plan

- Where no comparable treatment or outcome measures are available, manufacturers must work with KOLs, regulators and HTA bodies to agree appropriate measures
- Where head-to-head trials are not feasible, agree alternatives to generating comparative data
- Where only single-arm trials are feasible, agree how historical controls or baseline comparisons may be leveraged
- Where surrogate endpoints will be used, agree selection and validation
- Where long-term claims will be made, explore:
  - The type of modelled data that could be used to bridge the evidence gap
  - Acceptable approaches for dealing with data uncertainty at the time of launch

Developers need to establish first which value story secures commercial viability; HTA/payer advice informs the corresponding evidence requirements

Identify the commercially viable target price and population

Develop a value story that supports the target price in the target population

Create an evidence generation plan that provides the best possible support for the value story

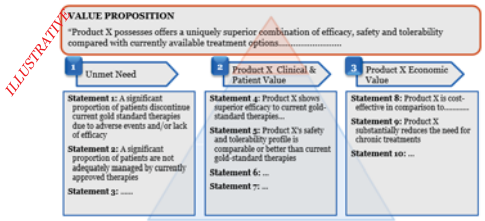
HTA/Payer Consultation

Contextualise learnings and revisit evidence generation plan

In order to engage constructively with HTA bodies/ payers the following activities should be conducted sequentially:

- Understand the value drivers for a given therapy and how these can help support a commercially viable price and volume opportunity; this forms the basis for the development of the target value story
- Develop the *briefing document*, for the consultation addressing:
  - The unmet need in the target therapy area
  - The product's target value story and how it addresses the unmet need
  - The evidence generation plan, and how this supports the target value story
  - The areas where evidence gaps may exist, and formulate questions for HTA bodies and propose potential solutions
- Explore the HTA bodies' perspective on how to best substantiate the target value story, and adjust the evidence generation plan accordingly

We employ secondary and primary research and health economic modelling to frame the value story and corresponding evidence requirements that support commercial viability



- The value story is typically structured in three domains, with an overarching paragraph that summarises the value proposition
  - **Value proposition:** Summary of incremental value of novel therapy over existing standard of care
  - **Value statements:**
    - Unmet need: it should align with the incremental benefits of the novel therapy
    - Clinical and economic value statements: describe therapy's incremental benefit in clinical and economic terms
      - Value statements should be supported by the proposed clinical and economic evidence to be generated

The outputs from the activities described so far inform the development of the target product profile (TPP) and evidence generation plan

Activity	Output	Objective
Headroom for innovation	Validate that target indication/ therapeutic position can accommodate a high cost therapy	Ensure commercial viability
Pricing research and sensitivity analysis	Identify key clinical and economic drivers of product value to incorporate into TPP	
	Define product performance and manufacturing cost thresholds for commercial viability	
Clinical feasibility analysis	Understand feasibility of undertaking clinical development in target indication / therapeutic position	Ensure feasibility of running clinical trial
Engage with payers (and regulators)	Ensure agreement on therapeutic position with regulators Ensure evidence generation plan in line with expectations of regulators and key market access stakeholders	Ensure appropriateness of evidence generation plan

In preparation for launch, we focus on maximising the commercial potential in terms of price, access and revenue

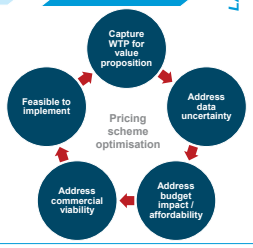
(Pre-clinical) Shaping early development → (Pre-pivotal) Opportunity optimisation → (Pre-launch) Tactical pre-launch preparations → LAUNCH

- Address clinical data gaps through data modelling where appropriate
- Finalise the health economic models
- Populate the value dossier including the value story and supporting clinical and economic evidence (customised to individual market requirements) in preparation for submission
- Identify the target price for each launch market and geographical launch sequence
- Develop strategies for maximising reimbursement and adoption potential
  - Innovative pricing schemes/Managed Entry Agreements (MEAs)
  - Post-launch evidence generation plans
- Detail the readiness of the healthcare delivery system (e.g. available infrastructure and treatment pathway) to assess potential constraints and need for pocess re-engineeiring and investment

Innovative pricing mechanisms can help address data uncertainty and affordability concerns for payers

(Pre-clinical) Shaping early development → (Pre-pivotal) Opportunity optimisation → (Pre-launch) Tactical pre-launch preparations → LAUNCH

- We help manufactures identify the optimal pricing scheme on the basis of the following considerations:
  - Scheme reflective of therapy value and willingness-to-pay (WTP)
  - Minimises implications of data uncertainty
  - Enables payer affordability
  - It is commercially viable for the manufacturer
  - It is feasible to implement within a given healthcare system without creating significant administrative burden



Methodologies and case studies

Understanding the challenges and opportunities presented by the existing pricing and reimbursement (P&R) frameworks is key

Main levers used in P&R processes in select European markets

UK
- Cost-utility analysis (CUA)
- Budget impact analysis (BIA)

France
- ASMR 1-3 (moderate to major improvement):
  - International price referencing (EU4)
  - CUA
- ASMR 4-5 (minor or no improvement):
  - Domestic comparator price
- Price-volume agreements

Germany
- With added benefit:
  - Price premium over domestic comparator price
  - Budget impact

  If price negotiation fails then arbitration:
  - International price referencing (EU15)

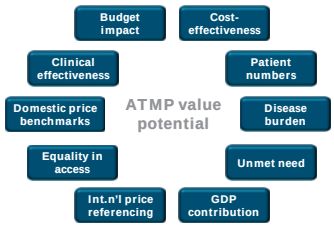
    Potentially followed by:
  - Efficiency frontier analysis
- No added benefit:
  - Domestic comparator price

The CGT Catapult's HE&MA team leverages more than 30 years' experience in international pharmaceutical pricing and reimbursement

ATMPs present unique value propositions that challenge traditional pricing and reimbursement frameworks

- The frameworks used to assess conventional pharmaceuticals are well suited for valuing smaller, incremental improvements in health benefit
- However, using these frameworks to assess potentially game-changing therapies like ATMPs is more challenging, e.g. how to value:
  - One-off therapy with long-term benefits
  - Potential lifetime cure

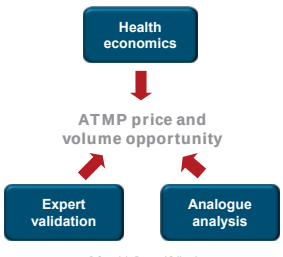
....while managing uncertainty



We leverage multiple methodological frameworks in exploring and optimising the value potential of ATMPs across different countries

- **Health economics:**
  - Cost-effectiveness and budget impact analyses
  - Sensitivity analyses, extrapolation and regression analyses
  - Data uncertainty management
- **Analogue analyses:**
  - Secondary research of relevant HTA and commissioning decisions to elicit willingness to pay and adopt
- **Expert validation:**

  Interviews with payer and clinician experts to:
  - Determine willingness to pay and affordability
    - Via qualitative/ quantitative pricing methodologies
  - How to maximise adoption potential through optimisation of value proposition, evidence generation plan, and innovative pricing and reimbursement schemes
  - Detail the need for NHS process re-engineering and clinical infrastructure to facilitate adoption



Health technology assessments (HTAs) in most countries use some form of cost-effectiveness analysis to determine value for money

- **Cost-effectiveness analysis (CEA)** framework compares the incremental cost to the incremental health benefit of different therapies, i.e. answering the question *how much better is the new therapy in terms of health benefit, and how much more do we have to pay?*

$$\frac{\text{Lifetime cost of new therapy} - \text{Lifetime cost of standard of care}}{\text{Lifetime benefit of new therapy} - \text{Lifetime benefit of standard of care}} = \text{Incremental cost-effectiveness ratio (ICER)}$$

...however, how benefits are measured differs between territories

- **Cost-utility analysis (CUA):** Is a form of CEA where the health benefit is measured as Quality-Adjusted Life Years (QALYs)
  - QALYs reflect the life expectancy (life years) and quality of life (utility, ranging from 0-1) experienced during that period

- **Other CEAs:** health benefit can be measured in a number of different ways, e.g.
  - Life years gained
  - Events avoided
  - Other relevant clinical outcomes

The CUA framework forms the basis for two analytical approaches use in shaping the early development of ATMPs

We use the CUA framework to

Prioritise between target patient groups (where several therapeutic targets exist)

- Identify the indication with the greatest commercial opportunity (in terms of maximum revenue potential of "cure") as per:
  - *The headroom for innovation* (maximum lifetime value of displacing current standard of care and maximising patients' potential health benefit)
  - Maximum patient numbers (i.e. 100% market share of target population)

Define parameters for commercial viability

- Identify product performance and manufacturing cost thresholds for commercial viability
  - Define 'go'/'no-go' decision-making criteria for the R&D stage-gates
  - Through sensitivity analysis identify key value drivers to inform the early stage Target Product Profile (TPP) and evidence generation plan

Case study 1: Deciding on which patient group to target is one of the most important strategic decisions in pre-clinical development

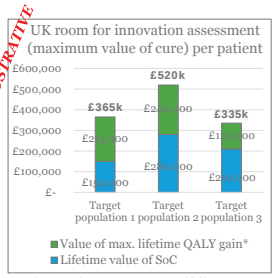
- The choice of indication or therapeutic position needs to be driven by both clinical and commercial considerations
- We enable developers compare the commercial opportunities presented by different target patient groups through:
  - **A. The headroom for innovation analysis:** estimating the maximum price potential per patient treated (i.e. "the value of cure"), using the cost-utility analysis (CUA) framework
  - **B. The size of the target population:** the maximum volume opportunity (100% market share)
- A and B are subsequently used to determine which indication presents the greatest commercial opportunity in terms of the maximum revenue potential

The outputs from our analyses allow developers to identify:

- The target population that should be prioritised in the planning of the development programme
- The target population that is likely to be the best candidate for subsequent indication extension

Case study 1: We identify the target population with the greatest commercial potential by estimating the maximum revenue potential

ILLUSTRATIVE



- The **headroom for innovation** analysis allows us to discern how the lifetime value of the SoC and the maximum potential health improvements differ between the three target groups
- We estimate the **maximum revenue potential** for the three target populations by multiplying the maximum value of cure per patient with the maximum number of patients (assuming 100% market share)

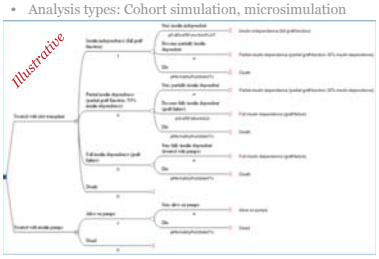
Max. value of cure/ patient	×	Max. number of patients	=	Max. revenue potential
£365k		1,200		£438 million
£520k		1,800		£936 million
£335k		1,100		£368 million

* Using WTP/QALY as per NICE guidelines

We use country-specific adaptions to extend this analysis to other countries that use the CUA framework to inform price potential

Once the target population is identified, we establish the interrelationship between levels of efficacy and commercial viability through more detailed health economic modelling

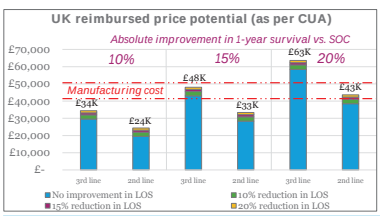
- Model types employed: Decision tree, state transition Markov model, discrete event simulation, transmission model
- Analysis types: Cohort simulation, microsimulation



- Health states & transitions: as per disease trajectory
- The time horizon of the analysis is typically lifetime (up to 100 yearly cycles / discounted)
- Each health state is assigned cycle-specific costs and outcomes (e.g. QoL in CUA)
- Sensitivity analyses can address uncertainty
  - Deterministic: univariate/ multivariate
  - Probabilistic: parametric/ non-parametric (bootstrapping)
  - Structural

Case study 2: We assess the impact of a range of efficacy scenarios and therapeutic positions on UK price potential and commercial viability

- We tested different scenarios of therapeutic positions in an acute condition (2nd and 3rd line) and relevant outcomes
- Survival and therapeutic positioning had the biggest impact on the reimbursed price potential

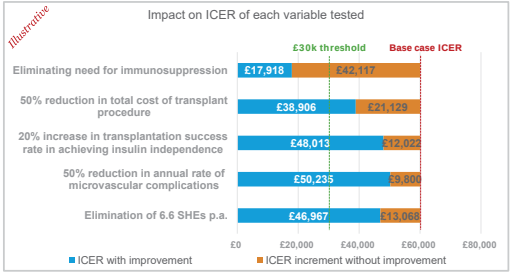


This formed the basis for the value story and the planning of data generation activities:

- Early Target Product Profile (TPP) development
- Clinical development specifications
  - Target therapeutic position
  - Trial inclusion criteria
  - Outcome measures for value maximisation
- Product performance and manufacturing cost thresholds for commercial viability; criteria for 'go'/'no-go' Stagegate decisions
- Financial forecasts providing confidence to management and investors

Case study 3: Sensitivity analysis identifies key value drivers and focus areas for R&D and evidence generation to strengthen value proposition

One-way sensitivity analysis for an islet transplantation therapy in type 1 diabetes



ICER: Incremental cost-effectiveness ratio; SHEs: Severe hypoglycaemic events

A crucial part of assessing the price potential is identifying the willingness to pay (WTP) for improvements in health benefit

Cost-utility analysis (CUA) countries:

- The WTP/QALY improvement is only explicitly stated in a small minority of countries where the CUA framework is used
  - E.g. the National Institute for Health and Care Excellence (NICE) in England has explicitly defined WTP/QALY values depending on the degree of data uncertainty, how effectively QoL has been captured, how innovative the therapy is, whether it is an end of life therapy, the size of the target population and the number of QALYs gained
- In most countries using CUA, the WTP/QALY is not explicitly stated, however, recent HTA and pricing decisions can give an indication

Countries using other CEAs:

- In countries that do not use the CUA, it is necessary to establish
  1. The most relevant measure of health improvement to use in the CEA, and
  2. The WTP per unit improvement in that measure
- The WTP in these cases are rarely explicit, and it is necessary to employ both secondary and primary research to elicit what an appropriate price premium is for a given improvement in health

To assess WTP when not explicitly stated in the public domain, we use analogue analyses and primary research with key market access stakeholders (expert validation)

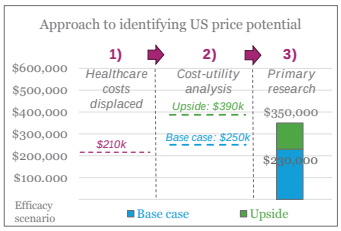
Engagement with key market access stakeholders is used to provide multiple insights

Explore, validate, inform:

- The WTP for improvements in health benefit as identified through analogue analysis
- The price potential identified through health economic modelling
- The budget impact and its implications on adoption
- Strategies that mitigate risk, maximise value proposition and adoption through:
  - Optimisation of value story and evidence generation plan
  - Minimisation of consequences of data uncertainty and facilitating affordability through innovative pricing schemes
  - Accounting and planning for clinical infrastructure requirements and NHS process reengineering (where relevant)

Case study 4: In markets where CUA plays a lesser role in HTAs, we identify price potential through a triangulation of pricing frameworks

- We used the triangulation approach to assess the US price potential for a novel ATMP using two efficacy scenarios (base case and upside)
- Triangulation of pricing frameworks:
  1) Secondary research into relevant pricing benchmarks; identification of healthcare costs associated with the SOC and anticipated to be displaced by the new therapy
  2) CUA to explore potential for price premium over displaced costs
     - WTP thresholds were informed by the Institute for Clinical and Economic Review's methods
  3) Primary research with key US market access stakeholders to validate and inform the above



- We also explored formulary inclusion considerations and how they vary between public and private insurers, value optimization, risk-mitigation and adoption maximization strategies

Budget impact (BI) assessments are commonly used by payers to quantify the aggregate impact of introducing a novel therapy

- Key drivers:
  - Change in costs per patient from displacing existing therapies (usually healthcare budget only)
  - Number of patients treated
  - Time horizon (≤5 years)
- England operates a budget impact 'test', which assesses whether a new therapy's aggregate additional cost to the healthcare budget exceeds the threshold value of £20 million per year
  - If the £20 million threshold level is exceeded, additional commercial negotiations and potential restrictions apply

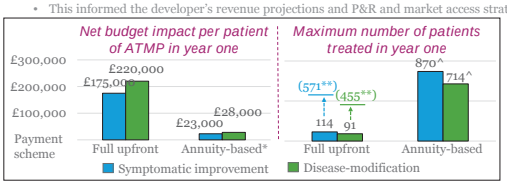
Illustrative exemplar of a novel budget neutral therapy

BUDGET IMPACT

		Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Total Population of England	50,542,505						
Target population p.a.	1,000						
SOC price per patient	£5,000						
New Therapy price per patient	£6,000						
Probability of rehospitalisation with SOC	2.00%						
Probability of rehospitalisation with New Therapy	1.00%						
Cost per rehospitalisation	£20,000						
Market share of New Therapy		0%	20%	40%	60%	80%	100%
SOC Costs		£5,000,000	£4,000,000	£3,000,000	£2,000,000	£1,000,000	£0
New Therapy Costs		£0	£1,200,000	£2,400,000	£3,600,000	£4,800,000	£6,000,000
Total Drug Costs		£5,000,000	£5,200,000	£5,400,000	£5,600,000	£5,800,000	£6,000,000
Rehospitalizations Avoided		0	10	20	30	40	50
Reduction in Rehospitalization Costs		0	£200,000	£400,000	£600,000	£800,000	£1,000,000
Change in Costs							
Change in Drug Costs		£0	£200,000	£400,000	£600,000	£800,000	£1,000,000
Change in Rehospitalization Costs		£0	-£200,000	-£400,000	-£600,000	-£800,000	-£1,000,000
Total Change in Costs		£0	£0	£0	£0	£0	£0

Case study 5: We use budget impact analyses to understand how different pricing schemes may affect affordability and uptake

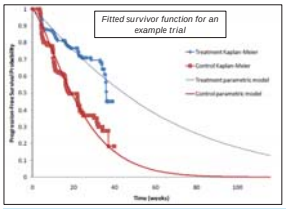
- Budget impact analyses (BIAs) assess overall affordability, which can impact price and volume potential in all markets, but nowhere is this relationship defined more explicitly than in England
- We used CUA to assess the UK price potential for a novel ATMP, and subsequently used BIA to understand the potential volume implications under the net budget impact 'test'; we showed how performance-based annuity payments can increase volumes at launch (as compared to a full upfront payment) without triggering further commercial negotiations
  - This informed the developer's revenue projections and P&R and market access strategy



* Using maximum price potential identified through CUA divided by five years (the assumed duration of the annuity scheme)
** Over five years
^ Maximum number of patients in years one through five (as annuity payments are split over five years)

Case study 6: We apply regression analysis to bridge the evidence gap between short-term trial data and long-term value claims

- We apply the methods provided by NICE's Decision Support Unit*
- Specified parametric models are fitted
  - Exponential, Weibull, Gompertz, log-logistic, log normal, generalised Gamma
- Optimal model selected based on statistical considerations and external validity

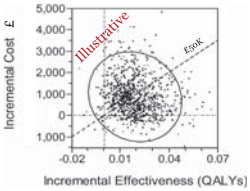


- Sensitivity analysis is undertaken using alternative plausible models
- The resulting degree of uncertainty depends on:
  - The relative length of the extrapolated period vs. the observation period
  - The ability to validate extrapolated data on the basis of biological plausibility, predictive surrogate markers, clinical expert opinion etc.

*NICE Decision Support Unit Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data, March 2013

Case study 7: We quantify uncertainty metrics to support the cost-effective price determination

1. Probability of not exceeding the ICER threshold (based on probabilistic sensitivity analysis (PSA); % iterations ≤ICER threshold)
   - o No defined threshold: ~70% probability of being CE is considered of low uncertainty
2. Incremental Net Health Effect (NHE) expressed in monetary or QALY terms; it is the mean value across all iterations i.e.



Incremental NHE =[(Incremental Effectiveness) x (ICER threshold)] –[Incremental Costs]

The NHE should be positive for adoption; the greater, the more likely

3. Incremental NHE at population level and over the technology time-horizon

Case study 8: Calculating the consequences of decision uncertainty is another way of addressing data uncertainty

Consequences of Decision Uncertainty
(calculated according to the Expected Value of Perfect Information framework)

Illustrative

Scenarios (PSA iterations)	Treatment Net Health Effect (NHE) in terms of QALYs		Optimal Choice	Opportunity Loss when choosing B vs. A (in QALYs)
	Treatment A	*Treatment B*		
1	9	12	B	0
2	12	10	A	2
3	14	20	B	0
4	11	10	A	1
5	14	13	A	1
Mean value across all scenarios	**12**	**13**	**B**	**0.8**

Consequences of decision uncertainty at individual patient level
- This can be calculated at population and technology time-horizon level
- No defined threshold; relative magnitude in comparison to NHE is key

Case study 9: The uncertainty metrics can help us identify the optimal Managed Entry Agreement

Illustrative

Scenario	ICER	Incremental NHE QALY *	Probability Cost Effective	Consequences of decision uncertainty QALY *	Adoption potential
£100,000 one-off acquisition cost per patient	£50,000	-55	50%	300	Very low
10% discount	£45,000	200	65%	250	Low
Pay-for-performance: *payment only for patients with remission by day 30*	£40,000	250	70%	100	Possible
Lifetime leasing: *payment on a monthly basis as long as patient remains alive (£2,000 pcm)*	£35,000	1,000	99.5%	2	High

Maximise *Minimise*

Pricing scheme that optimises uncertainty metrics

*Based on end-of-life ICER threshold: £50,000

Case study 10: We developed a framework for quantifying administrative cost of outcomes-based reimbursement (OBR)

- The methodological framework was developed with input from a Project Advisory Group of NHS stakeholders and representatives from NICE
- Respondents detailed the tasks and activities related to four implementation phases across various pricing schemes for a given therapy

Pricing scenario	Set-up	Intervention	Monitoring	Exit
Full upfront payment				
Annuity		*Cells to be populated through research*		
Rebate				
Other				

- The data was categorised by task, time required to complete the task, job band, and capital investment, before grouping by hospital departments
- Participants provided their respective job bands, and time resource was costed using the mid-point salary from the NHS Pay Scales
- The results were reported as cost (£s) and time; per implementation phase; total and incremental costs; direct and indirect costs
  - o Direct costs: relating to 'per patient activity' (mainly variable costs)
  - o Indirect costs: not patient number-sensitive, e.g. set-up costs and infrastructure that is required for the system to run (mainly fixed costs)

P. Kefalas, et al. (2018) *Establishing the Cost of Implementing a Performance-Based, Managed Entry Agreement for a Hypothetical CAR T-cell Therapy*

Case study 10: We applied this framework to the hypothetical CAR T-cell therapy assessed by NICE, using a staged payment OBR scheme over 10 years

- The scenario with OBR is associated with a less mature data set, while the scenario without OBR, the therapy is assumed to have more mature data
- The time horizon of the OBR scheme is assumed to be 10 years, and 50 new patients were assumed to be treated each year
- The focus of the analysis is the administrative burden (the therapy cost and associated patient management costs were excluded)

Incremental administrative burden of introducing a CAR T-cell therapy *with* an OBR

Comparator	Total (10 years)		Per year	
	£	Time	£	Time
SoC	£1,814	11 days	£181	1.1 days
CAR T-cell therapy w/o OBR	£2,403	15 days	£240	1.5 days

Key learnings:
- In the context of a gene therapy with a likely price tag in the hundreds of thousands of pounds, the incremental administrative cost per patient seem reasonable (i.e. £181 per patient per year compared to the SoC)
- Most of the additional administrative costs stem from the additional monitoring for OBR
  - o The monitoring phase represent 87% of the additional cost, 58% of which are concentrated in year 1 (due to greater number of blood tests to address the uncertainty around safety and efficacy)
  - o 56% of the additional costs are in the pharmacy department, due to the requirement for additional pharmacy personnel time and the higher salary band for this type of personnel

P. Kefalas, et al. (2018) *Establishing the Cost of Implementing a Performance-Based, Managed Entry Agreement for a Hypothetical CAR T-cell Therapy*

Case study 11: Assessing the appropriateness of the NHR for facilitating outcomes-based reimbursement (OBR)

- We used secondary and primary research to explore how the National Haemoglobinopathy Registry (NHR) can facilitate OBR in thalassaemia

Key findings:

Opportunities	Challenges
Many key data points recorded: • Blood transfusion frequency • Iron chelation therapy given • Mortality • Number of hospital admissions • Complications and serious adverse events	Key data points currently not recorded (in NHR): • Blood haemoglobin levels (proxy for anaemia) • Stem cell transplantation data • Units of blood transfused
	Annual reporting of data (meaning OBR schemes need to be on annual time horizons)
Completion rates ~90%	No official completion rate data
	Staff shortages are a barrier to complying with data entry
Future funding to incentivise higher completion rates	Patient reluctance to grant NHR access to data

Key learnings
- The NHR in its current form only partially provides the framework needed to enable OBR
  - o Not optimal for implementing patient-level reimbursement schemes, schemes that require more frequent than yearly readings and/or outcomes not currently recorded
- NHR can be a vehicle for cohort-level OBR with annual intervals based on e.g. transfusion independence, if:
  - o The appropriate staff resource is provided
  - o There is a successful drive towards ensuring all patients have their data recorded
- Being able to leverage NHR as the data collection infrastructure for OBR in thalassaemia depends on:
  - o NHS England's current restructuring efforts being successful in increasing data entry compliance and improving patient consent rates to sharing data
  - o Creation of additional data fields

For full case study, please see: https://ct.catapult.org.uk/case-study/appropriateness-nhr-facilitating-performance-based-reimbursement-thalassaemia-%E2%80%93-current

添付資料3　引用・複写を禁ずる。

nibrt
The National Institute for Bioprocessing Research and Training

Welcome to NIBRT

10th January 2020

Agenda

10 AM	Introductions
10:15 AM	Overview of NIBRT to include: ▪ Overview of the organization, background, objectives, staffs, and budget size ▪ Specific contents of the training program ▪ Participant background and cost ▪ Outcomes/ Achievement (including how to evaluate) ▪ Relationship with national industrial development ▪ Relationship with industry like GE
11 AM	Tour of NIBRT
11:45 AM	Discussion over working lunch
12:15 PM	Meeting close

Questions

- Outline of the biopharmaceutical industry promotion policy in EU, and the relationship with other party (ex EMA/EU,NIIBLE/USA)
- The overview and features of the University, especially the relationship with universities (“eco-system”).
- Could you tell me the relationship of pharmaceutical industry?
- Budget size, number and position of researcher and facilities, such as; bioreactors and their operating status.
- The development of new training programs; area (gene &cell therapy etc.)and the number of program types /training period
- The total number of people educated.

Introduction to NIBRT

Principle “*…Much depends on the skills, training and attitudes of the personnel involved…*”

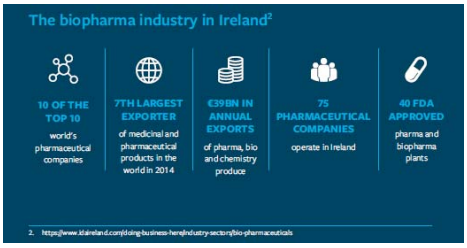
The Rules Governing Medicinal Products in the European Union
ANNEX 1: MANUFACTURE OF STERILE MEDICINAL PRODUCTS

Who we are

- NIBRT is a world-class institute, based in Dublin, Ireland whose mission is to deliver training and research solutions for the global biopharmaceutical manufacturing industry
- Opened in 2011, NIBRT’s research and training building (6,500m²) features state-of-the-art pilot scale manufacturing facilities
- Established with IDA Ireland, to promote world-class biopharma investment in Ireland
- www.nibrt.ie / LinkedIn / Twitter @NIBRT_/ YouTube

2018: A Year in Review https://www.youtube.com/watch?v=MALmCQtxEEA
Introduction to NIBRT https://www.youtube.com/watch?v=IKNDec7mvvY

What we do



Mission: to support the development of the biopharma industry by providing world class research and training solutions in state-of-the-art facilities

- Train and educate over 4,000 people annually to work in all areas of bioprocessing
- Collaborate with industry on scientific research to drive biopharma innovation
- Support major biopharma investment in Ireland
- Provide a test bed for new technologies and processes

2018: By the numbers

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Our Facilities

- Laboratory scale aseptic processing, cell bank, inoculum and protein purification suites.
- Upstream Suite: 1 x 30 litre and 2 x 150 litre stainless steel bioreactors and 200L single use STR, perfusion system, disc stack centrifuge, depth (stainless steel and single use) and micro-filtration skids.
- Downstream Suite: 2 x ultrafiltration/diafiltration automated systems, 2 x automated process chromatography systems, automated column packing technologies, viral inactivation vessels and a number of integrity test stations.
- Fill-finish suite: a vial filling machine under LAF and RABS with associated preparation room and aseptic gowning room, a modular aseptic workstation with integral HPV bio-decontamination.
- Manufacturing Support: Buffer and media preparation suites utilising both stainless steel and disposable technologies; equipment preparation including parts washer and autoclave.
- Central clean utilities suite including highly purified water, clean steam and CIP skids and clean air generating systems
- Suite of analytical laboratories for product and process characterization.
- The NIBRT-GE Single-Use Centre of Excellence is run by NIBRT, and GE is the technology provider delivering a fully integrated biomanufacturing platform based on single-use technologies to the centre.
- Prometheus NT.48 (Nanotemper Technologies), Labchip (Perkin Elmer), Milliflex membrane filtration system (Merck), Endotoxin reader (Lonza), Biotrak particle counter (PMT). NEW FOR 2019

- The NIBRT facility (6,500 m2) is a purpose-built, multi-functional building with extensive upstream, downstream, fill-finish, associated analytical facilities and process utilities.
- Operated in a realistic GMP simulated, operational manufacturing environment.
- 3D Virtual Tour of NIBRT: https://my.matterport.com/show/?m=BSzwUd8ToAs

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Awards

2012 Facility of the Year Awards SPECIAL RECOGNITION for Novel Collaboration

2012 BioProcess AWARDS

Medicine Maker 100 Power List 2016

2016 BioProcess AWARDS NOMINEE

Pharma Manufacturing Awards FINALIST

Pharma Industry Awards 2016 Partnership Alliance of the Year WINNER

Analytical Scientist 50 XX Power List 2016

Pharma Industry Awards 2016 Pharma Education & Training Award WINNER

Pharma Industry Awards 2017 Kuehne + Nagel WINNER Partnership Alliance of the Year

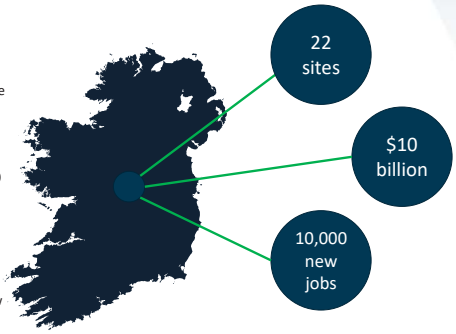
Growth of Biopharma in Ireland

2009-2019: A decade of growth

2018 Announcements include:

- **AbbVie** Expands Oncology Capability at the Company's Site in Ballytivnan, Sligo
- **MSD** is to develop a new biotechnology facility in Dublin, with the expected creation of up to 350 new jobs
- **Takeda** to invest €25m and create up to 70 new roles
- **WuXi Biologics** to Invest €325 million to Build Largest Biomanufacturing Facility Using Single-use Bioreactors
- **BioMarin** Expands its Cork Facility to add Drug Product Filling capability
- **MSD** - new investment will create 170 new jobs

https://www.youtube.com/watch?v=aCffReWhL_8&feature=youtu.be



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Client Testimonials 1

Kieran McAtamney *Construction Manager, Jacobs*	*"Great course delivered by NIBRT Team of Aoife, Adam and Melissa"*
Aidan Quinn *Springboard Student*	*"May I first take this opportunity to thank you and your colleagues at NIBRT and IT Sligo for your professionalism, support, guidance and patience during our Biotechnology Processing certificate course this year! The online lectures and lab practical's gave a great insight and understanding to a complex and very interesting subject and I believe participation in the course will greatly improve my job prospects."*
Margaret Stagg *Alexion*	*"NIBRT provided me with great insight into the Biopharmaceutical industry. It's a great facility to be able to see first-hand what the day to day activates with a bio site could be My training with NIBRT was the driving force behind my transition from 20 years manufacturing experience with Hewlett Packard to my current role with Alexion. I am currently still studying and will be attending two lab practical days next week. Looking forward to it."*
Associate Vice President *Keytruda Quality at Merck*	*"Excellent Training opportunity. The instructors were highly educated, experienced and engaged every one of us by delivering even the most complicated material in an easily understood format. The combination of theoretical and hands on training in this state of the art facility is an absolute necessity for anyone seeking to gain insight into bioprocessing."*
Paddy Gleeson *HR Director, Takeda Dunboyne Biologics*	*"NIBRT is a critical support as we built up our organisation and facility to deliver life changing medicines for our rare disease patients."*
Aleksander Kostrzewski *Student on L7 Bioprocessing Engineering NIBRT program*	*"Congratulations on pharma awards. It's another proof that we are learning from the best in the industry."*

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Client Testimonials 2

Nicolas Pivet *General Manager, Global Services, GE Healthcare*	*"NIBRT is an amazing institute, the place to stop by when working in the Bioprocessing space, with an impressive and growing global reach."*
Caroline Brady *Global Commercial Operations Leader GE Healthcare*	*"Fantastic couple of days spent at NIBRT. Particular thanks to John for a great tour of the facility. Really impressive setup!"*
Maria Aldridge *Quality Specialist at AbbVie*	*"Great few days of training on Upstream Processing at NIBRT National Institute for Bioprocessing Research and Training this week via The Institute of Technology, Sligo."*
David Weil *Applications Scientist at Agilent Technologies*	*"Great work also being done on how E and L compounds in bioprocessing can impact final products."*
Alison Wilson *Personal Development Coach at Anova Coaching*	*"It was great to see the exceptional facilities you have to support training in our industry."*
Eva Fahey *NIBRT TY Student*	*"I was one of the TY students you accepted to take part in a Biopharmaceutical Training week in NIBRT from the 29th of January to the 2nd of February. Thanks so much for taking me again for that week as I enjoyed so much and I can honestly say it has been a highlight of my transition year."*

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Training

"Tell me and I forget, teach me and I remember, involve me and I learn"

Benjamin Franklin

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2018: Training Clients

SANOFI GENZYME, Bristol-Myers Squibb, PSC, M2i, Allergan, MSD Be well, ALEXION, ROQUETTE, alvotech, Pfizer, 3M, Agilent, the compliance group, ChromaCon, ENGINEERS IRELAND, Baxter, collen 200, M-W GROUP, sartorius stedim, aerie, BioReliance, abbvie, PAUL, Shire, VWR, Rentschler Biopharma, eurofins, AMGEN, Takeda, accenture, BIOMARIN, CHEMSOURCE, JACOBS, PALL Pall Corporation, Thermo SCIENTIFIC

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NIBRT's "6C's Training Model"

2018
- 4,300 trainees
- 18,200 learning days
- Over 100 courses delivered

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NIBRT's role in Workforce Development

Pre hire → Post hire

Higher education programmes
- ✓ Graduates
- ✓ MSc courses
- ✓ European Industrial Doctorate, Horizon 2020

Workforce readiness programmes
- ✓ Springboard
- ✓ Skillnets

Policy
- ✓ Biopharma Industry Training Group
- ✓ BioPharmaChemical Ireland:
  - Action Plan for Biopharma Skills and Jobs

Careers Events
- ✓ NIBRT *Careers in Biopharma*
- ✓ CareerZoo
- ✓ Company Careers Days

Public Engagement/Awareness
- ✓ Schools
- ✓ Branding
- ✓ Biopharma Ambition

Continuous Professional Development
- ✓ Short courses
- ✓ Workshops, seminars, events
- ✓ Education programmes
- ✓ Online

Customised Training
- ✓ Amgen case study
- ✓ MSD case study
- ✓ BMS case study
- ✓ Shire/Takeda case study

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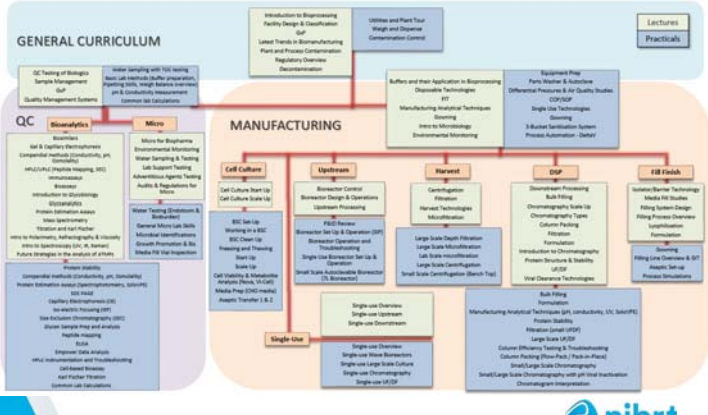
NIBRT Curriculum



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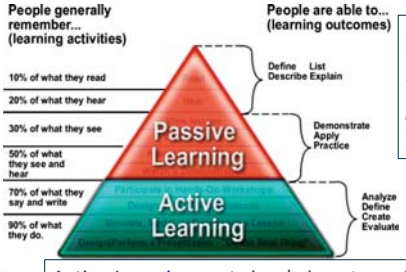
Learning Methods - NIBRT Teaching Philosophy



Learning is not a spectator sport. Students do not learn much just by sitting in class listening to teachers, memorizing pre-packaged assignments, and spitting out answers. They must talk about what they are learning, write about it, relate it to past experiences, apply it to their daily lives. ***They must make what they learn part of themselves.*** Arthur W. Chickering and Zelda F. Gamson

Active Learning, put simply is not passive, preferably not didactic, not mere note taking etc.. Ideally it provides a shift from the teacher or facilitator 'doing' to the student 'doing'. Thus it involves the ***learner engaging*** in activities that will support and stimulate 'higher-order' thinking, problem solving and ideally critical analysis.

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NIBRT Training Solutions

Type	Description	Methodology	Accreditation
1. Short courses	Short courses of 1-2 days duration on key topics	▪ Classroom ▪ Practicals	Not accredited
2. NIBRT Online Academy	Online portal of short modular training courses	▪ Online	Not accredited
3. Customised courses	All aspects of the courses are customised to meet a client's particular requirements	▪ Classroom ▪ Practicals	Can be accredited if required
4. Continuous Professional Development	Part-time education programmes delivered in partnership with Irish Universities	▪ Online ▪ Classroom ▪ Practicals	Yes
5. Masters	Part-time *MSc in Bioprocessing Science*	▪ Online ▪ Practicals	Yes

Further information: https://www.nibrt.ie/training-and-education/

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Short Courses

Further information: https://www.nibrt.ie/training-and-education/training-courses/

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Case Study: Amgen

AMGEN®

- Amgen's Global Qualification Improvement Programme
- Video case study: https://www.youtube.com/watch?v=y5bQ6ZO0puE
- Customised training programmes for Amgen Manufacturing staff from USA and Puerto Rico.
  - ✓ Cell Culture
  - ✓ Downstream processing
  - ✓ Formulation and Fill Finish

"Its through better process understanding and trouble shooting techniques that I learnt at NIBRT that I feel much more qualified and I'm excited to take these learnings back to my team at Amgen"

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Case Study: Takeda Dunboyne Biologics*


THE IRISH TIMES

Invest in Ireland AWARDS

Pharma group Shire signs training deal for Dublin

Irish domiciled company to get 'customised training programmes' from universities

about 16 hours ago

Shire

Susan Hynes, Dunboyne site lead for Shire and Dominic Carolan, CEO NIBRT. Photograph: Conor McCabe

*Previously Shire

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Case Study: BMS

- Customised training of BMS staff
- BMS Skillnets Programme
- Hosting of BMS MS+T team
- Research collaboration with BMS and vendors
- Careers events: https://www.youtube.com/watch?v=yDF7lvGO8k

Bristol-Myers Squibb

Springboard+

- Free accredited training programmes for those looking to work in biopharma industry
- 90% funded for those in employment
- NIBRT trains approx. 400 Springboard students per year, 60% are new entrants to the industry
- Courses from level 6 to level 9
- https://www.nibrt.ie/training-and-education/springboard/

SPRINGBOARD+ www.springboardcourses.ie

EUROPEAN UNION Investing in your future European Social Fund

Rialtas na hEireann Government of Ireland

HEA HIGHER EDUCATION AUTHORITY AN tÚDARÁS um ARD-OIDEACHAS

FUTURE JOBS IRELAND

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Single Use Centre of Excellence

- In June 2017, GE and NIBRT opened the Single Use Centre of Excellence to further develop biopharma manufacturing skills and expertise in Ireland and internationally.
- Seed Train Scale Up: ReadyToProcess / WAVE 25 Rockers and Pilot Scale up Capabilities: Xcellerex™
- Downstream Protein Purification / Two ÄKTA ready systems for isocratic use and an additional ÄKTA with gradient capability
- Filtration: ÄKTA ReadyFlux
  https://www.youtube.com/watch?v=GfNgoOQ3A_E

GE Healthcare

Emerson Room at NIBRT

Announced in Q1 2018, the NIBRT Emerson Control Room will provide automation and control training, education and research solutions based on Emerson's Delta V platform.

Next courses:
- September 10-13th 2019: DeltaV Implementation I
- September 16-19th 2019: DeltaV Systems Batch Implementation

EMERSON.

NIBRT Online Academy (NOA)

The NIBRT Online Academy (NOA) went live in October 2019.
NOA offers a constantly updated library of interactive, eLearning training courses on key aspects of biopharma manufacturing. Courses can be accessed online on a range of devices to provide "just in time" learning in an engaging, stimulating format.

https://noa.nibrt.ie

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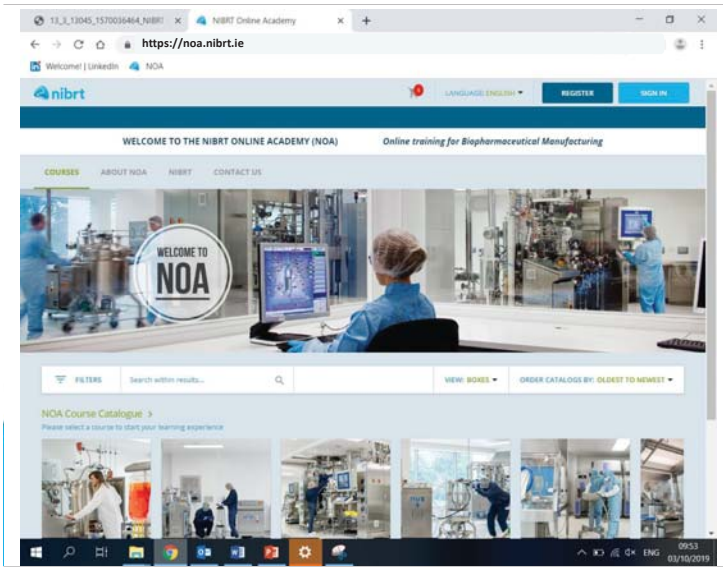

NIBRT Online Academy (NOA)

- Courses are typically 45mins in duration.
- Courses contain a range of multimedia such as voice over, animation, 3D models to maximise learning retention.
- A Course Completion Certificate is issued upon successful completion of the course test, which requires an 80% pass rate.
- Courses are priced at €99 for 30 days access with volume licensing options available.
- Courses can be taken across a range of devices, PC, laptop, tablet with mobile access available form Q1 2020.
- NOA is fully SCORM compliant.
- New courses are added on a quarterly basis.
- Contact killian.odriscoll@nibrt.ie to discuss any aspect of NOA.

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NOA Courses: release dates

NOA Courses: release dates		
October 2019	*January 2020*	*April 2020*
Biotechnology and Biopharmaceuticals	Cell Biology and Recombinant DNA Technology	Fermentation in Biopharmaceutical Manufacturing
Overview of Biopharmaceutical Manufacturing	Bioreactors in Bioprocessing	Downstream Processing: Centrifugation
Cell Culture in Biopharmaceutical Manufacturing	Downstream Processing: Ultrafiltration and Diafiltration	Aseptic Processing - Gowning
Downstream Processing: Protein Purification - Chromatography	Freeze Drying	Aseptic Processing – Decontamination and Sterilization Technologies
Formulation in the Biopharmaceutical Industry	Aseptic Processing – Contamination Control	Clean In Place
Aseptic Processing – Concepts and Controls	Process Validation: Process Qualification and Control	Aseptic Processing - Cleanrooms and Control Technologies
Process Validation: Process Design		

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Biopharma 4.0 Alliance

NIBRT in partnership with the Boston Consulting Group (BCG) have established the *Biopharma 4.0 Alliance* which provides the platform, capabilities and expertise needed to deliver a step change in performance through smarter adoption of disruptive Industry 4.0 technologies.

Throughout 2019, a digital demonstrator is being established in NIBRT to provide an immersive training experience, which will allow participants from across the biopharma industry and beyond to experience new 4.0 technologies (such as AR, VR, robotics, data visualisation) first hand.

https://www.youtube.com/watch?v=A9X2KRxG3sI

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Global Partners Programme

"Tell me and I forget, teach me and I remember, involve me and I learn"

Benjamin Franklin

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NIBRT Global Partners Programme

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Jefferson University, Philadelphia

THE IRISH TIMES

Tue, Feb 27, 2018

NIBRT teams up with US college for $10m biologics facility

NIBRT to collaborate with university to train about 2,500 people annually at new centre

Kathy Gallagher of Jefferson University, Minister Heather Humphries and Dominic Carolan, chief executive of NIBRT

https://www.siliconrepublic.com/careers/nibrt-jefferson-institute-bioprocessing

brt

Jefferson Institute for Bioprocessing

- The Jefferson Institute for Bioprocessing (JIB) creates a unique value proposition and educational opportunity for Jefferson to support the 900+ biopharmaceutical-related companies in the northeast.
- The JIB is a specialized education and training institute for single-use-reactor bioprocessing technology used in modern biopharmaceutical manufacturing.
- Opened: 31st May 2019
- http://www.eastfalls.jefferson.edu/jib/
- https://www.youtube.com/watch?v=Gy0mji5er0U

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Global Partners Programme

- The *Global Partner Programme* outlines a flexible phased approach which NIBRT can implement with international organisations to provide training and education capability in their region.
- The *Global Partner Programme* operates on a franchise type model, where NIBRT can provide set-up and ongoing support to Partners in each of the following areas:
  - Facility design input
  - Equipment list / vendor recommendation
  - Business and operating model development
  - Branding, marketing
  - Business development with global biopharmas
  - Curriculum design, development, delivery
  - Train-the-trainer
  - Membership of NIBRT *Global Partner Programme*
- Partners are responsible for
  - Capital and operational funding
  - Management and operation of the Partner training operation to agreed quality standards
- Ongoing membership of the *Global Partner Programme* provides continuous support including:
  - Annual curriculum updates and new course development
  - Ongoing business development with global biopharmas and vendors
  - Annual Global Partners meeting in NIBRT
  - Speaking opportunities at NIBRT partner events such as CPHI, Bioprocess International
  - Preferred access to NIBRT's training and research events
  - Collaboration opportunities with NIBRT Research
  - Discounted rates for NIBRT Contract Bioanalytical Services and Process Development

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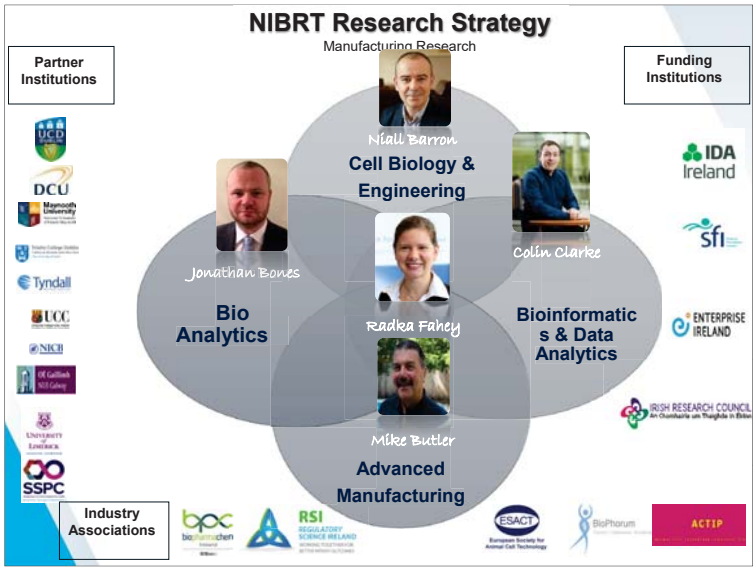
Phased Approach

Phase	Deliverables	Date	Cost
Initial Discussions	▪ Non Disclosure Agreement ▪ NIBRT visit to Partner ▪ MOU signed by both parties (Sept 2019)	Sept 2019	No charge
Planning	NIBRT to provide input on: ▪ Building design, specification and drawings ▪ Equipment list and recommendations ▪ Market intelligence and financial expertise to draft Business Plan and operating model ▪ Curriculum Design ▪ Branding and marketing guidelines Partners to provide: ▪ Approved Business Plan and Funding within a defined timeline Full Commercial Contract signed by both parties	TBC	TBC
Implementation	*See next slide*		
Ongoing support	*See next slide*		

Research



Collaboration Mechanisms

A wide variety of funding opportunities for example:

- Industry provides 10% cash and 20% benefit-in-kind, with balance of 70% funding provided via Enterprise Ireland Innovation Partnerships
- Large scale collaborations possible via a variety of schemes such as Disruptive Technology Innovation Funds, SFI, EU

Intellectual property managed in accordance with National IP Guidelines
http://www.knowledgetransferireland.ie

Case Study: Siemens

- Siemens "MindSphere" platform – open IoT based platform
- Establishment of a new biopharma application centre in Ireland
- €5 million investment over 4 years
- Team based in NIBRT and Siemens Ireland
- https://www.youtube.com/watch?v=nf96HhYnyaw

SIEMENS
Ingenuity for life

Case Study: ThermoFisher Scientific

ThermoFisher SCIENTIFIC

- In 2016, Thermo Fisher Scientific, and Dr Jonathan Bones, NIBRT announced a scientific collaboration focused on the development of analytical solutions for the characterisation of complex biopharmaceuticals.
- This collaboration will see NIBRT develop workflows on the Thermo Scientific biomolecule column range.
- https://www.thermofisher.com/ng/en/home/industrial/pharma-biopharma/pharma-biopharma-learning-center/biopharmaceutical-characterization-information/nibrt-collaboration-information.html
- https://www.youtube.com/watch?v=NRIUPqY6YFE

Case Study: Pfizer

- The development and application of advanced process and analytical methods for in-line monitoring and continuous characterisation of bio-pharmaceutical manufacturing processes.
- Reduce the requirement for offline analytical testing by integrating automated sampling and analytical characterisation using high resolution liquid chromatography mass spectrometry directly with the bioreactor systems
- Generate both process and product quality data in near real time, to provide process and analytical scientists with key information to guide development of their bio-pharmaceutical processes

Winning in Europe

- Sept 2018: Dr Colin Clarke, will lead a prestigious *Marie Skłodowska-Curie European Industrial Doctorate programme*.
- €2.9 million four year project.
- The STACCATO research programme will develop state of the art single cell analysis methods to characterise the molecular heterogeneity of cell populations utilized in the biopharmaceutical industry.

Cell and Gene Therapies

Cell and Gene Therapies

- **Cell and Gene Therapy Forum** established in Dec 2018 to define and develop Ireland's value proposition for manufacture of Cell and Gene Therapies. Representatives from Industry, Government and Academia. **White Paper** to be published May 2019.
- **Takeda** Grange Castle manufacture of an allogeneic cell therapy approved for treating complications associated with Crohn's disease.
- **Legend** (CAR-T) have established a research presence in Dublin.
- NIBRT delivering **workforce development** programmes on Cell and Gene Therapy commencing Q3 2019.
- NIBRT research project (TBA) focused on **characterisation of viral capsids**.
- Centre for Cell Manufacturing at NUI Galway is a custom-built licensed centre designed to manufacture ATMPs such in **human clinical trials**.
- Academic research leaders include:
  - Prof Wang / UCD/ development of new DNA plasmid vectors for skin gene therapy
  - Prof Pete Humphries / TCD / molecular genetics of Retinitis Pigmentosa (RP)
- Developing indigenous companies, for example:
  - **Avectas** Raises $10 Million in Equity Finance
  - Trinity's Gene Medicine Spin-Off **Genable** Technologies Sold to Spark Therapeutics

Contract Services

Contract Bioanalytics

Analytical platforms provided by NIBRT Contract Research.

- Bioanalytical characterisation including sequence verification and coverage, PTM Analysis using intact protein and peptide centric approaches, glycosylation analysis including site occupancy and heterogeneity.
- New in 2018: Host Cell Protein Analysis, Hydrogen Deuterium Exchange Mass Spectrometry
- Test facilities for new technologies
- Process development